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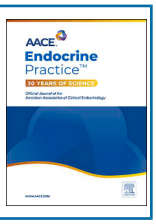

AACE Clinical Guidance

American Association of Clinical Endocrinology Consensus Statement Algorithm for Management of Adults With Type 2 Diabetes — 2026 Update

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Abbreviations: AACE, American Association of Clinical Endocrinology; Ab, antibody; ABCD, adiposity-based chronic disease; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; A1C, hemoglobin A1c; BG, blood glucose; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CDC, U.S. Centers for Disease Control and Prevention; CGM, continuous glucose monitoring; CHF, congestive heart failure; CIADM, checkpoint inhibitor-associated autoimmune DM; CK, creatine kinase; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DASH, Dietary Approaches to Stop Hypertension; DHA, docosahexaenoic acid; DKA, diabetic ketoacidosis; DM, diabetes mellitus; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; ER, extended release; FBG, fasting blood glucose; FDA, U.S. Food and Drug Administration; FPG, fasting plasma glucose; GIP/GLP-1 RA, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist; GLN, glinide or meglitanide; GMI, glucose management indicator; GV, glucose variability; HCP, health care professional; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; HTN, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IPE, icosapent ethyl; LADA, latent autoimmune diabetes of adults; LDL-C, low-density lipoprotein cholesterol; LV, left ventricle; mAb, monoclonal antibody; MACE, major adverse cardiovascular event; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MI, myocardial infarction; MODY, maturity-onset diabetes of the young; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; OGTT, oral glucose tolerance test; OSA, obstructive sleep apnea; PCSK9, proprotein convertase subtilisin/kexin type 9; PPG, postprandial glucose; RCT, randomized controlled trial; SAMS, statin-associated muscle symptoms; SGLT2i, sodium glucose cotransporter 2 inhibitor; SU, sulfonylurea; TG, triglyceride; TIA, transient ischemic attack; TIR, time in range; TZD, thiazolidinedione; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

Disclaimer: This document represents the official position of the American Association of Clinical Endocrinology on the subject matter at the time of publication. Subject matter experts who participated on the task force utilized their judgment and experience, supported by relevant scientific evidence as available. Every effort was made to achieve consensus among the task force members.

Consensus statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician. We encourage health care professionals to use this information in conjunction with their best clinical judgment. The guidance provided may not be appropriate in all situations. Any decision(s) by health care professionals to apply this guidance provided in this consensus statement must be made in consideration of local resources and individual patient circumstances.

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Objective: This consensus statement provides evidence-based visual guidance in graphic algorithms and a summary of evidence and considerations to assist health care professionals with the diagnosis and management of adults with prediabetes and diabetes mellitus in shared decision making to improve care.

Methods: The American Association of Clinical Endocrinology (AACE) selected a task force of medical experts to update the 2023 AACE Comprehensive Type 2 Diabetes Management Algorithm and align this algorithm update with related AACE clinical guidance.

Results: This algorithm for management of adults with type 2 diabetes (T2D) includes 11 sections: (1) Principles for the Management of Adults With T2D; (2) Prediabetes Algorithm (3) Diabetes Classification Algorithm (new); (4) Atherosclerotic Cardiovascular Disease Risk Reduction Algorithm: Dyslipidemia; (5) Atherosclerotic Cardiovascular Disease Risk Reduction Algorithm: Hypertension; (6) Comorbidities- and Complications-Centric Glycemic Control Algorithm; (7) Glucose-Centric Glycemic Control Algorithm; (8) Initiating and Titrating Insulin Algorithm; (9) Profiles of Pharmacotherapy for T2D; (10) Profiles of Pharmacotherapy for Obesity; and (11) Vaccine Recommendations for Adults With T2D.

Conclusions: This 2026 update emphasizes lifestyle modification and treatment of overweight/obesity as key pillars in the management of prediabetes and T2D. It also provides guidance on the management of atherosclerotic risk factors of dyslipidemia and hypertension. A new algorithm was added to ensure that other causes and classes of diabetes are considered beyond T2D. There continues to be an emphasis on a complications- and comorbidities-centric approach, beyond glucose levels, to frame decisions regarding first-line and subsequent pharmacological choices for treating adults with T2D.

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Introduction

The first iteration of the American Association of Clinical Endocrinology (AACE) algorithm for glycemic control was published in 2009 and expanded on the visual guidance provided by the American College of Endocrinology/AACE Diabetes Road Maps to help clinicians navigate the expanding classes of approved antihyperglycemic agents.[1,2] The next update of the type 2 diabetes (T2D) management algorithm was published in 2013 and incorporated new sections on the management of individuals with overweight/obesity, dyslipidemia, and hypertension (HTN).[3] Additional updates of the AACE T2D algorithm have been incorporated through 2023[4–9] based on scientific evidence and current clinical practice; the task force is grateful for the contributions and framework provided by previous authors (see Acknowledgments). The 2023 update of the T2D management algorithm[9] incorporated new approaches, including a comorbidities- and complications-centric approach to T2D pharmacotherapy, that aligned with the AACE Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan – 2022 Update.[10] This 2026 algorithm provides updated visual guidance for shared decision making in the management of adults with T2D, including a new algorithm for diabetes mellitus (DM) classification. To help implement the visual guidance, this accompanying consensus statement provides updated summaries of clinical considerations by incorporating the newest AACE guidance on obesity/adiposity-based chronic disease (ABCD)[11] and dyslipidemia[12,13] and the latest key clinical trial evidence (including SURMOUNT-2,[14] SURMOUNT-OSA,[15] SELECT, STEP-HFpEF DM,[16] SUMMIT,[17] FLOW,[18] SOUL,[19] ESSENCE,[20] and SYNERGY-NASH,[21] among others) that have resulted in expanded regulatory indications for glucose-lowering medications including for cardiorenal risk reduction, metabolic dysfunction–associated steatohepatitis (MASH), and obstructive sleep apnea (OSA).

AACE appointed a multidisciplinary task force to determine specific updates for each section of the algorithm. A proportion of 2023 T2D task force members were appointed to the 2026 task force for continuity and to ensure consistency in guidance that aligns with AACE positions. A methodology fellow and clinical guidance staff conducted searches to identify relevant peer-reviewed literature published since the development of the 2023 T2D algorithm,[9] prioritizing meta-analyses and systematic reviews, clinical practice guidelines, randomized controlled trials (RCTs), and observational studies of sufficient quality. Subgroups selected evidence to support specific algorithm subsections. The process for updating the algorithm involved multiple task force meetings between August 2024 and July 2025. The subgroups brought proposed changes to the complete task force for discussion and consensus.

This 2026 algorithm continues to emphasize lifestyle modification and treatment of overweight/obesity as key pillars in the management of prediabetes and T2D. There is a new addition, the DM classification algorithm, which is intended to remind clinicians to consider other causes of DM beyond T2D that can inform further investigation of secondary causes, natural history, and management strategies. The importance of appropriate treatment of atherosclerotic risk factors of dyslipidemia and HTN is highlighted. Given the publication of several new studies since 2023 regarding the benefit of antihyperglycemic medications on complications, the algorithm continues to stress a comorbidities- and complications-centric approach beyond glucose levels to frame decisions with updates regarding first-line and subsequent pharmacologic choices for the treatment of adults with T2D, as recommended in the 2022 AACE guideline update,[10] the 2023 AACE T2D algorithm,[9] and recommendations from other organizations.[22,23] However, the authors acknowledge that health care disparities and lack of access to newer medications and cost remain significant barriers for the optimal treatment of some individuals with T2D.

The algorithm is divided into sections that outline the principles for the management of adults with T2D (Algorithm Fig. 1), management of prediabetes and prevention of progression to T2D (Algorithm Fig. 2), diagnosis and classification of DM (new) (Algorithm Fig. 3), treatment of cardiovascular (CV) risk factors, dyslipidemia (Algorithm Fig. 4) and HTN (Algorithm Fig. 5), comorbidities- and complication-centric (Algorithm Fig. 6) and glucose-centric (Algorithm Fig. 7) approaches for glycemic control with pharmacotherapy, and insulin initiation and titration (Algorithm Fig. 8). Also included are updated tables that

PRINCIPLES OF THE AACE ALGORITHM FOR MANAGEMENT OF ADULTS WITH TYPE 2 DIABETES

1.	Lifestyle modification is the foundation for all therapy.
2.	Use a comprehensive approach for weight loss to achieve clinical goals.
3.	Choice of pharmacologic therapy is guided by glycemic targets and comorbidities (overweight/obesity, ASCVD, CHF, CKD, MASLD, OSA).
4.	Choice of therapy considers ease of use and access.
5.	Individualize glycemic targets (A1C, GMI, TIR, FBG, PPG).
6.	Optimal A1C (or GMI) is ≤6.5% (48 mmol/mol) or as close to normal as is safe and achievable.
7.	Avoid therapeutic inertia and get to goal as soon as possible (adjust ≤3 months).
8.	Avoid hypoglycemia.
9.	CGM is highly recommended to reach glycemic goals in adults with diabetes.
10.	Comorbidities and complications must be managed for comprehensive care.

Abbreviations: **A1C**, hemoglobin A1c; **ASCVD**, atherosclerotic cardiovascular disease; **CGM**, continuous glucose monitoring; **CHF**, congestive heart failure; **CKD**, chronic kidney disease; **FBG**, fasting blood glucose; **GMI**, glucose management indicator; **MASLD**, metabolic dysfunction-associated steatotic liver disease; **OSA**, obstructive sleep apnea; **PPG**, postprandial glucose; **TIR**, time in range

Algorithm Fig. 1. Principles of the AACE algorithm for management of adults with type 2 diabetes.

summarize the benefits and risks of medications for T2D (Algorithm Fig. 9) and obesity (Algorithm Fig. 10). Updated immunization guidance is provided that summarizes vaccine recommendations from the Advisory Committee on Immunization Practices of the U.S. Centers for Disease Control and Prevention (CDC) as they currently stand at the time of publication (Algorithm Fig. 11).

Algorithm 1. Principles of the AACE Algorithm for Management of Adults with T2D

Following are the principles of this algorithm developed by consensus for the management of adults with T2D (Algorithm Fig. 1).

Lifestyle Modification is the Foundation of All Therapy

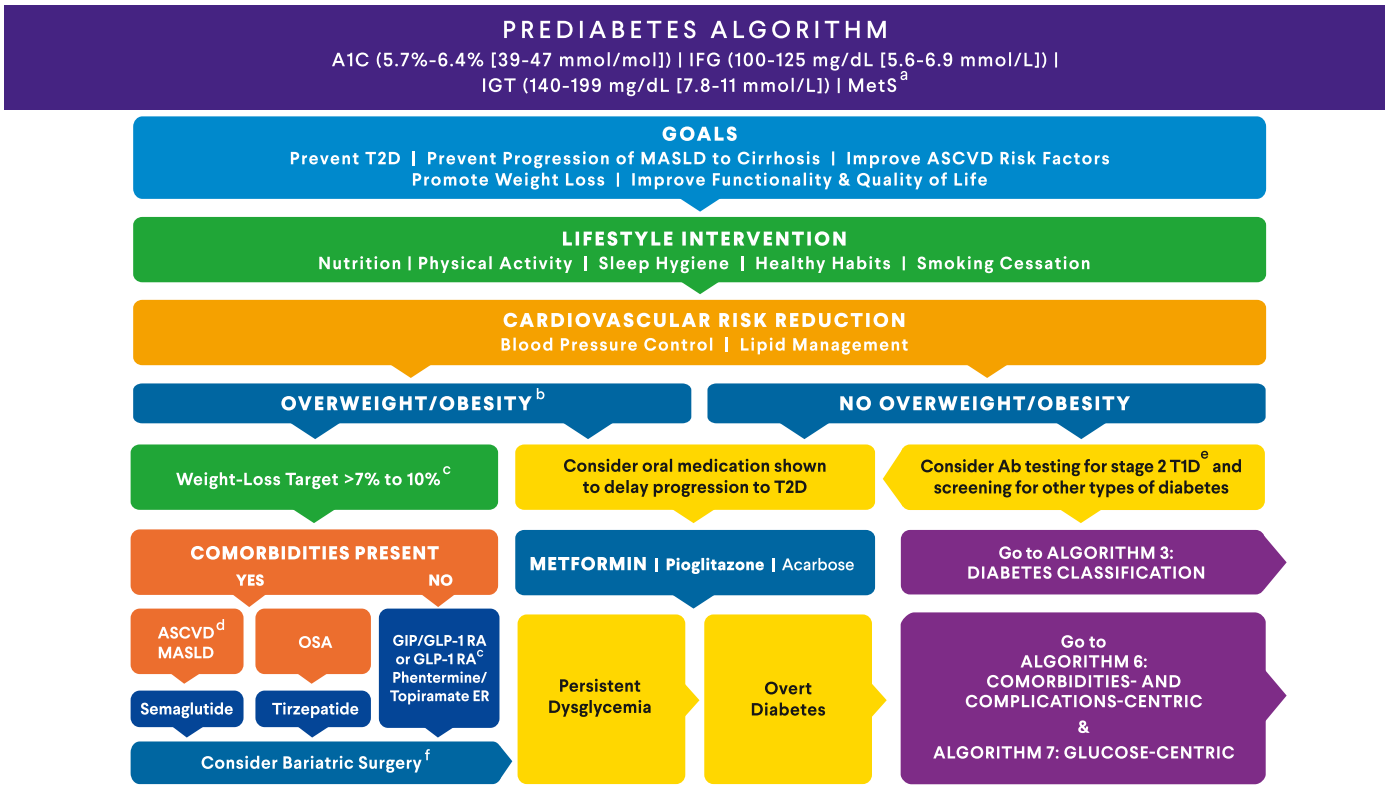
Lifestyle modification includes increased physical activity, healthy dietary changes, smoking and tobacco cessation, and reduced alcohol intake. Assessment of sleep hygiene and management of sleep disorders, including sleep apnea, sleep disruption, and insomnia, also are essential to optimize health. Mood disorders, DM distress, and internalized weight bias need to be addressed for optimal results.[24,25]

Use a Comprehensive Approach for Weight Loss to Achieve Clinical Goals

Excess weight results in insulin resistance and increases the risk of developing prediabetes and T2D. Lifestyle and pharmacologic intervention to achieve weight loss is a key pillar of the comprehensive treatment of adults with prediabetes to decrease progression to T2D. Excess weight also leads to multiple complications beyond dysglycemia that comprise ABCD[11,26,27] including dyslipidemia, elevated blood pressure (BP), atherosclerotic cardiovascular disease (ASCVD), metabolic dysfunction–associated steatotic liver disease (MASLD), OSA, and osteoarthritis. Weight loss may mitigate many of the cardiometabolic and biomechanical components of ABCD, albeit with varied thresholds ranging from >5% to >15% reduction in body weight.[28]

Choice of Antihyperglycemic Therapy is Guided by Glycemic Targets and Comorbidities (Overweight/Obesity, Congestive Heart Failure, Chronic Kidney Disease, ASCVD, MASLD, and OSA)

The armamentarium of antihyperglycemic agents has expanded over the past 2 decades beyond insulin secretagogues (sulfonylureas [SUs]/glinides [GLNs]), thiazolidinediones (TZDs), and metformin. Large prospective clinical trials have confirmed the varied glycemic efficacy of newer medical therapies including dipeptidyl peptidase 4 inhibitors (DPP-4is), sodium-glucose transporter 2 inhibitors (SGLT2is), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and glucose-dependent insulinotropic polypeptide/GLP-1 dual receptor agonists (GIP/GLP-1 RAs). Although glycemic control has an essential role in the prevention and decreased progression of T2D complications, there is accumulating evidence of the positive impact of individual T2D pharmacotherapies on comorbidities and complications beyond glycemic control, including for congestive heart failure (CHF), chronic kidney


PREDIABETES ALGORITHM
A1C (5.7%-6.4% [39-47 mmol/mol]) | IFG (100-125 mg/dL [5.6-6.9 mmol/L]) | IGT (140-199 mg/dL [7.8-11 mmol/L]) | MetS[a]
GOALS
Prevent T2D | Prevent Progression of MASLD to Cirrhosis | Improve ASCVD Risk Factors
Promote Weight Loss | Improve Functionality & Quality of Life
LIFESTYLE INTERVENTION
Nutrition | Physical Activity | Sleep Hygiene | Healthy Habits | Smoking Cessation
CARDIOVASCULAR RISK REDUCTION
Blood Pressure Control | Lipid Management
OVERWEIGHT/OBESITY[b]
NO OVERWEIGHT/OBESITY
Weight-Loss Target >7% to 10%[c]
Consider oral medication shown to delay progression to T2D
Consider Ab testing for stage 2 T1D[e] and screening for other types of diabetes
COMORBIDITIES PRESENT
YES
NO
METFORMIN | Pioglitazone | Acarbose
Go to ALGORITHM 3: DIABETES CLASSIFICATION
ASCVD[d] MASLD
OSA
GIP/GLP-1 RA or GLP-1 RA[c] Phentermine/ Topiramate ER
Semaglutide
Tirzepatide
Consider Bariatric Surgery[f]
Persistent Dysglycemia
Overt Diabetes
Go to ALGORITHM 6: COMORBIDITIES- AND COMPLICATIONS-CENTRIC & ALGORITHM 7: GLUCOSE-CENTRIC

[a]NCEP ATP III Criteria. [b]Lower BMI cut-off values for overweight and obesity may be applicable to individuals of Asian descent. [c]Indications for obesity medications are obesity or overweight BMI ≥27 kg/m^2 with ABCD complication(s) including prediabetes. Choose approved obesity medications that can achieve >7% to 10% weight loss, shown to reduce progression to T2D: injectable semaglutide, tirzepatide, phentermine/topiramate ER. Also consider other second-line approved obesity medications (phentermine [short term], orlistat, naltrexone-ER/bupropion-ER) if first-line not available. See also ALGORITHM 10: PROFILES OF PHARMACOTHERAPY FOR OBESITY. [d]History of myocardial infarction, stroke, or symptomatic peripheral arterial disease. Approved for MASH with moderate to advanced fibrosis. [e]Also consider screening for stage 2 T1D in individuals with prediabetes and personal and/or family history of autoimmunity regardless of BMI. Consider approved therapy available to delay progression to stage 3 T1D if positive. [f]Indications for bariatric surgery are BMI ≥40 kg/m^2 or ≥35 kg/m^2 with ABCD complication(s).

Abbreviations: **A1C**, hemoglobin A1c; **Ab**, antibody; **ABCD**, adiposity-based chronic disease; **ATP**, Adult Treatment Panel; **BMI**, body mass index; **ASCVD**, atherosclerotic cardiovascular disease; **ER**, extended release; **GIP**, glucose-dependent insulinotropic polypeptide; **GLP-1 RA**, glucagon-like peptide-1 receptor agonist; **IFG**, impaired fasting glucose; **IGT**, impaired glucose tolerance; **MASH**, metabolic dysfunction-associated steatohepatitis; **MASLD**, metabolic dysfunction-associated steatotic liver disease; **MetS**, metabolic syndrome; **NCEP**, National Cholesterol Education Program; **OSA**, obstructive sleep apnea; **T1D**, type 1 diabetes; **T2D**, type 2 diabetes

Algorithm Fig. 2. Prediabetes algorithm.

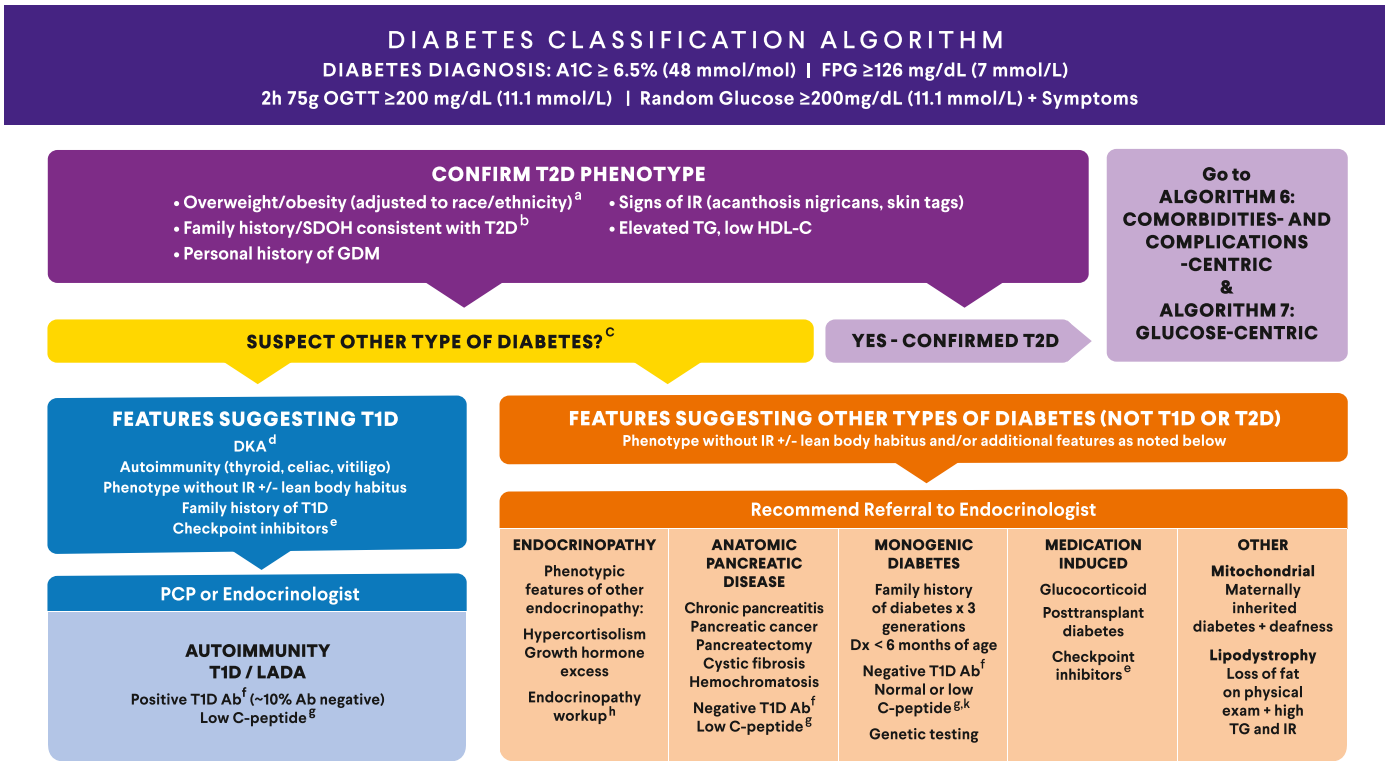
disease (CKD), ASCVD, MASLD, and OSA, depending on the medical therapy. Rather than use a uniform pharmacologic approach, clinicians should prioritize the coexistence of these frequently associated conditions to personalize the selection of T2D medications, using those that have evidence for improved outcomes for the accompanying comorbidities. The updated Comorbidities- and Complications-Centric Glycemic Control Algorithm (Algorithm Fig. 6) provides recommendations for pharmacotherapies that can be considered as first-line for adults with T2D that have CHF, CKD, risk for or preexisting ASCVD, history of stroke/transient ischemic attack (TIA), and MASLD. The Profiles of Pharmacotherapy for T2D table (Algorithm Fig. 9) also summarizes key aspects of the benefits and risks of available treatments from this perspective.

Choice of Therapy Considers Ease of Use and Access

Ideally, decision making regarding the prescription of antihyperglycemic agents, insulin analogs, and obesity treatments should be based on what is most likely to benefit individuals with T2D, balanced with the risks and potential side effects. However, barriers to access including availability, cost, insurance coverage, and formularies need to be considered, and this is acknowledged in the Glucose-Centric Glycemic Control Algorithm (Algorithm Fig. 7) and the Profiles of Pharmacotherapy for T2D (Algorithm Fig. 9) and Obesity (Algorithm Fig. 10). The impact of polypharmacy and increased medication burden, with use of multiple glucose-lowering agents and therapies for comorbidities, needs to be considered for each individual.

Individualize Glycemic Targets (Hemoglobin A1c, Glucose Management Indicator, Time in Range, Fasting Blood Glucose, and Postprandial Glucose)

Hemoglobin A1c (A1C) is a convenient and universally understood measure of glycemic control in the clinical setting. A1C should be measured every 3 months when not at goal and a minimum of twice per year in adults at goal. However, A1C also has limitations. It can be misleading (ie, falsely high or low) in some populations, including people with altered red blood cell lifespan, hemoglobinopathies, CKD, and some racial backgrounds.[29-31] Alternative methods of assessing glucose control may be helpful in these specific clinical scenarios. A1C also cannot provide information on short-term glucose variability (GV) and excursions that have been associated with a greater risk of T2D complications.[32-39] With the wider application of continuous glucose monitoring (CGM), additional glucose parameters have been shown to correlate with T2D outcomes. Increased time in range (TIR) has been shown to correlate with decreased microvascular complications.[32] It is recommended that TIR (glucose


DIABETES CLASSIFICATION ALGORITHM
DIABETES DIAGNOSIS: A1C ≥ 6.5% (48 mmol/mol) | FPG ≥126 mg/dL (7 mmol/L)
2h 75g OGTT ≥200 mg/dL (11.1 mmol/L) | Random Glucose ≥200mg/dL (11.1 mmol/L) + Symptoms
CONFIRM T2D PHENOTYPE
• Overweight/obesity (adjusted to race/ethnicity)[a]
• Family history/SDOH consistent with T2D[b]
• Personal history of GDM
• Signs of IR (acanthosis nigricans, skin tags)
• Elevated TG, low HDL-C
Go to ALGORITHM 6: COMORBIDITIES- AND COMPLICATIONS -CENTRIC & ALGORITHM 7: GLUCOSE-CENTRIC
SUSPECT OTHER TYPE OF DIABETES?[c]
YES - CONFIRMED T2D
FEATURES SUGGESTING T1D
DKA[d]
Autoimmunity (thyroid, celiac, vitiligo)
Phenotype without IR +/- lean body habitus
Family history of T1D
Checkpoint inhibitors[e]
PCP or Endocrinologist
AUTOIMMUNITY T1D / LADA
Positive T1D Ab[f] (~10% Ab negative)
Low C-peptide[g]
FEATURES SUGGESTING OTHER TYPES OF DIABETES (NOT T1D OR T2D)
Phenotype without IR +/- lean body habitus and/or additional features as noted below
Recommend Referral to Endocrinologist
ENDOCRINOPATHY
Phenotypic features of other endocrinopathy:
Hypercortisolism
Growth hormone excess
Endocrinopathy workup[h]
ANATOMIC PANCREATIC DISEASE
Chronic pancreatitis
Pancreatic cancer
Pancreatectomy
Cystic fibrosis
Hemochromatosis
Negative T1D Ab[f]
Low C-peptide[g]
MONOGENIC DIABETES
Family history of diabetes x 3 generations
Dx < 6 months of age
Negative T1D Ab[f]
Normal or low C-peptide[g,k]
Genetic testing
MEDICATION INDUCED
Glucocorticoid
Posttransplant diabetes
Checkpoint inhibitors[e]
OTHER
Mitochondrial
Maternally inherited diabetes + deafness
Lipodystrophy
Loss of fat on physical exam + high TG and IR

[a]Lower BMI cut-off values for overweight and obesity may be applicable to individuals of Asian descent. [b]A strong family history of obesity and diabetes in multiple family members and SDOH increases the likelihood of T2D versus other types (eg, monogenic diabetes). [c]Despite appropriate therapy and adherence, glucose levels remain above target. [d]DKA should prompt evaluation for T1D. DKA also can occur with a T2D phenotype (eg, ketosis-prone diabetes). [e]Checkpoint inhibitor–associated autoimmune diabetes may be Ab positive (50%), with low C-peptide, often presenting with DKA, and requires insulin therapy independent of Ab status and is irreversible. [f]T1D Ab: glutamic acid decarboxylase Ab, IA-2 Ab, zinc transporter 8 Ab and insulin Ab (if insulin naïve). Corticosteroids or immunosuppression may mask Ab positivity. [g]Check concomitant glucose for C-peptide interpretation (glucose >72 mg/dL [>4 mmol/L]). C-peptide is suppressed with hypoglycemia and severe hyperglycemia/DKA. May need to repeat C-peptide assessment for clarification of Dx. [h]Unexpected degree of insulin resistance especially with features of hypercortisolism or acromegaly. [k]C-peptide declines in most monogenic diabetes (eg, HNF1α may require insulin later in course).

Abbreviations: **A1C**, hemoglobin A1c; **Ab**, antibody; **BMI**, body mass index; **DKA**, diabetic ketoacidosis; **Dx**, diagnosis; **FPG**, fasting plasma glucose; **GDM**, gestational diabetes; **HDL-C**, high-density lipoprotein cholesterol; **HNF1α** , hepatocyte nuclear factor-1-alpha; **IR**, insulin resistance; **LADA**, latent autoimmune diabetes in adults; **OGTT**, oral glucose tolerance test; **PCP**, primary care physician; **SDOH**, social determinants of health; **T1D**, type 1 diabetes; **T2D**, type 2 diabetes; **TG**, triglycerides

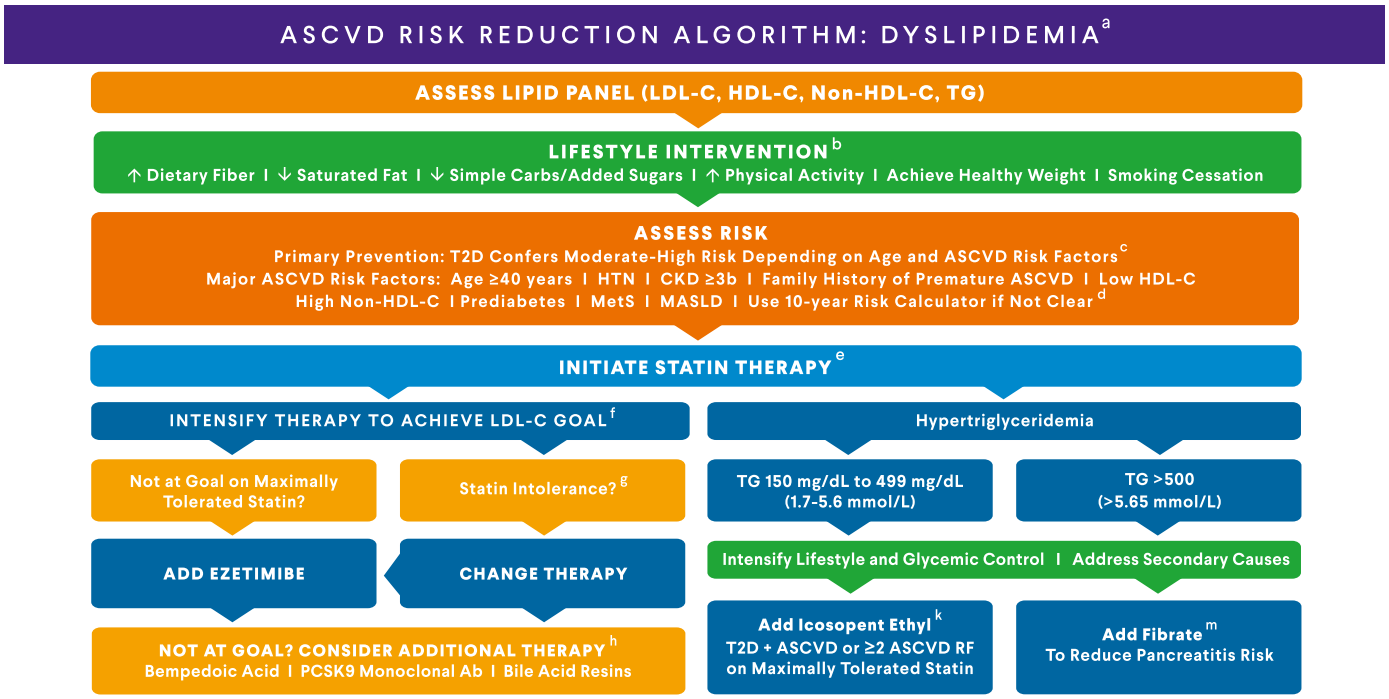
Algorithm Fig. 3. Diabetes classification algorithm.

range 70–180 mg/dL or 3.9–10 mmol/L) be >70%, combined with minimal time below range (TBR) (<4% for <70 mg/dL [<3.9 mmol/L] and <1% for <54 mg/dL [<3 mmol/L]) with <25% time above range for >180 mg/dL (>10 mmol/L) and <5% for >250 mg/dL (>13 mmol/L).[32,40-42] CGM generates the glucose management indicator (GMI), or "estimated A1C," which can be of some value as a surrogate for A1C, particularly when A1C is expected to be inaccurate (eg, anemia, hemoglobinopathies) or when there is discordance with A1C and data from glycemic monitoring, as with CKD.[43,44] CGM reports also include GV (calculated from % coefficient of variation = standard deviation of glucose/mean glucose × 100). Although the ideal threshold for GV is debated, a percent coefficient of variation of <33% is recommended for individuals who are taking insulin as lower values are associated with a reduced risk of hypoglycemia. When available, these alternative glucose parameters can be incorporated for monitoring and adjustment of therapy.

Optimal A1C (or GMI) is ≤6.5% (48 mmol/mol) or as close to normal as is safe and achievable

For most adults, an A1C of ≤6.5% (48 mmol/mol) should be targeted.[10] Achieving this A1C goal may require targeting fasting plasma glucose (FPG) to <110 mg/dL (<6.1 mmol/L) and 2-hour postprandial glucose (PPG) to <140 mg/dL (<7.8 mmol/L).[10] The impact of tight glycemic control for the prevention and/or decreased progression of microvascular and microangiopathic complications of T2D is well established.[45-47] Although there are epidemiologic data supporting an association of A1C and CVD and all-cause mortality on a continuum,[48] early clinical trial data did not provide evidence for mitigation of negative macrovascular disease outcomes with intensive glucose lowering. However, the increased rate of hypoglycemic events with attempted intensive glycemic control may have confounded the trials.[49] Pharmacologic therapies that have a lower risk of hypoglycemia and have proven efficacy in cardiovascular outcomes trials (CVOTs), particularly GLP-1 receptor agonists (GLP-1RAs) and SGLT2is, may allow for stricter glycemic control. However, the key word is "safe" with consideration of person-specific characteristics that would lead to the recommendation of a less stringent A1C target (eg, 7%–8% or 53–64 mmol/mol), including the following[10,46,47,50,51]:

- Limited life expectancy
- Elevated hypoglycemia risk and hypoglycemia unawareness
- Severe or multiple comorbid conditions (advanced CKD and established CVD)
- Long T2D disease duration with impediments to attaining a more stringent A1C goal
- Prohibitive cognitive and/or psychological status


ASCVD RISK REDUCTION ALGORITHM: DYSLIPIDEMIA[a]
ASSESS LIPID PANEL (LDL-C, HDL-C, Non-HDL-C, TG)
LIFESTYLE INTERVENTION[b]
↑ Dietary Fiber I ↓ Saturated Fat I ↓ Simple Carbs/Added Sugars I ↑ Physical Activity I Achieve Healthy Weight I Smoking Cessation
ASSESS RISK
Primary Prevention: T2D Confers Moderate-High Risk Depending on Age and ASCVD Risk Factors[c]
Major ASCVD Risk Factors: Age ≥40 years I HTN I CKD ≥3b I Family History of Premature ASCVD I Low HDL-C
High Non-HDL-C I Prediabetes I MetS I MASLD I Use 10-year Risk Calculator if Not Clear[d]
INITIATE STATIN THERAPY[e]
INTENSIFY THERAPY TO ACHIEVE LDL-C GOAL[f]
Not at Goal on Maximally Tolerated Statin?
Statin Intolerance?[g]
ADD EZETIMIBE
CHANGE THERAPY
NOT AT GOAL? CONSIDER ADDITIONAL THERAPY[h]
Bempedoic Acid I PCSK9 Monoclonal Ab I Bile Acid Resins
Hypertriglyceridemia
TG 150 mg/dL to 499 mg/dL (1.7-5.6 mmol/L)
TG >500 (>5.65 mmol/L)
Intensify Lifestyle and Glycemic Control I Address Secondary Causes
Add Icosopent Ethyl[k]
T2D + ASCVD or ≥2 ASCVD RF on Maximally Tolerated Statin
Add Fibrate[m]
To Reduce Pancreatitis Risk

[a]See also **2025 AACE Algorithm on Management of Adults with Dyslipidemia**. [b]Diets shown to decrease ASCVD risk include Mediterranean, DASH, plant-based. [c]T2D alone confers moderate to high risk. High risk: Age 20 to 39 years with ≥2 RF or ≥40 years with ≥1 RF. Very High risk: Known ASCVD or ≥40 years with end organ damage. [d]Risk calculators are intended for primary ASCVD prevention. 10-year risk calculators include Framingham, AHA PREVENT, PAHO HEARTS (Latin American and Caribbean), SCORE2 (European), SCORE2-Diabetes, ACC PCE, QRISK. For secondary prevention, individuals with known ASCVD (coronary, cerebral, and/or peripheral vascular disease) should be treated with high-intensity statin (atorvastatin 40-80 mg, rosuvastatin 20-40 mg). Consider dual therapy for individuals with acute coronary syndrome. [e]Majority of individuals with T2D will have indications for a high-intensity statin for primary prevention. [f]Achieve 50% reduction in LDL-C with goal <70 mg/dL (<1.8 mmol/L) for T2D with ≥1 ASCVD RF. [g]Statin intolerance: Consider drug interactions. Correct underlying contributors (VitD deficiency, hypothyroidism). Try alternative statin with lower incidence of myopathy (eg, hydrophilic: rosuvastatin/pravastatin) or decrease dose and frequency. [h]Choose add-on agents with the best evidence for reducing ASCVD risk. Not all add-on agents decrease ASCVD risk despite LDL-C with goal lowering. Inclisiran is FDA-approved for LDL-C reduction but is not currently recommended by AACE for ASCVD risk reduction due to insufficient CVD outcomes data at this time. Some therapies only have regulatory approval in those with established ASCVD (alirocumab). [k]IPE for established ASCVD or T2D and ≥2 RF with TG >150 mg/dL (>1.7 mmol/L) on maximally tolerated statin with LDL-C at goal. AACE recommends EPA alone rather than DHA + EPA formulations. [m]Prevention of pancreatitis is a treatment priority for TG >885 mg/dL (10 mmol/L). Olezarsen is approved to reduce TG for familial chylomicronemia as an adjunct to a low-fat diet.

Abbreviations: **Ab**, antibody; **ACC**, American College of Cardiology; **AHA**, American Heart Association; **ASCVD**, atherosclerotic cardiovascular disease; **CAC**, coronary artery calcium; **CKD**, chronic kidney disease; **DASH**, Dietary Approaches to Stop Hypertension; **DHA**, docosahexaenoic acid; **EPA**, eicosapentaenoic acid; **FDA**, U.S. Food and Drug Administration; **HDL-C**, high-density lipoprotein cholesterol; **HTN**, hypertension; **IPE**, icosopent ethyl; **LDL-C**, low-density lipoprotein cholesterol; **MASLD**, metabolic dysfunction-associated steatotic liver disease; **MetS**, metabolic syndrome; **PAHO**, Pan American Health Organization; **PCE**, pooled cohort equations; **PREVENT**, Predicting Risk of Cardiovascular Disease Events; **PSCK9i**, proprotein convertase subtilisin-kexin type 9 inhibitor; **RF**, risk factor; **SCORE**, Systematic Coronary Risk Evaluation; **T2D**, type 2 diabetes; **TG**, triglycerides; **VitD**, vitamin D3.

Algorithm Fig. 4. Atherosclerotic cardiovascular disease risk reduction algorithm: dyslipidemia.

Avoid therapeutic inertia and get to goal as soon as possible (adjust ≤3 months)

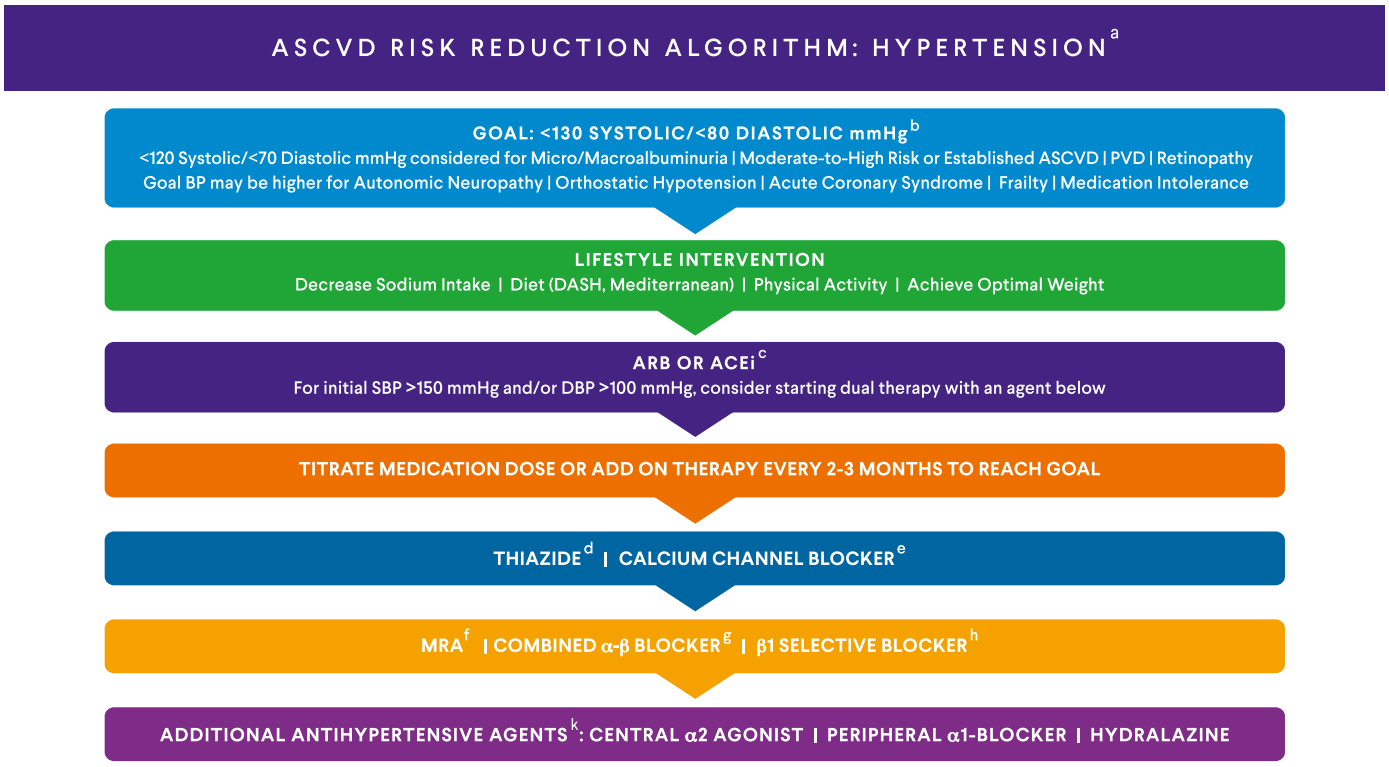
Therapeutic inertia—the failure of clinicians to escalate therapy or initiate new therapies—is a major threat to achieving improved health outcomes in individuals with overweight/obesity, prediabetes, and T2D.[52,53] There is evidence that achievement of early and intensive glycemic control positively impacts micro- and macrovascular complications of T2D in the long term, referred to as the legacy effect.[54-56] Clinicians should continuously evaluate treatment goals at each visit, ideally ≤3 months, and consider making therapeutic changes to more rapidly achieve targets for glucose, lipids, and BP. In some circumstances, it may be important to consider starting >1 pharmacotherapy at the time of diagnosis to meet the goals more rapidly, such as with marked hyperglycemia and HTN.

Avoid hypoglycemia

Hypoglycemia, defined as blood glucose (BG) <70 mg/dL (<3.9 mmol/L), is associated with an increased risk for adverse outcomes including mortality.[47,49] Therefore, the optimal treatment for adults with T2D should include consideration of the risk of hypoglycemia. Pharmacotherapy and A1C goals should be chosen to avoid hypoglycemia (see also Principles 5 and 6).[10] Metformin, TZDs, and newer agents such as DPP-4i, GLP-1RA, GIP/GLP-1RA, and SGLT2i have a lower risk of hypoglycemia, compared with SUs and insulin, and are preferred as initial therapy, in the absence of extreme hyperglycemia, to achieve optimal glycemic goals as recommended in the Glucose-Centric Glycemic Control Algorithm (Algorithm Fig. 7) and the Profiles of Pharmacotherapy for T2D (Algorithm Fig. 9).

CGM is highly recommended to reach glycemic goals in adults with diabetes

CGM has provided a major advance in the treatment of people with all forms of DM. For those with T2D, and who are taking basal insulin, clinical trials have shown that CGM is associated with increased TIR, improved A1C, and decreased hypoglycemia, including severe hypoglycemic events.[57-60] CGM is a valuable adjunct to T2D treatment including for all individuals on multiple-dose insulin (≥3 injections/day) or an insulin pump as well as those who have frequent or severe hypoglycemia, nocturnal hypoglycemia, or hypoglycemia unawareness who would benefit from warnings regarding glucose trends.[42] CGM may also engender behavioral or lifestyle changes (eg, increased physical activity, improved food choices), although further research is needed in this area.[61-68]


ASCVD RISK REDUCTION ALGORITHM: HYPERTENSION[a]
GOAL: <130 SYSTOLIC/<80 DIASTOLIC mmHg[b]
<120 Systolic/<70 Diastolic mmHg considered for Micro/Macroalbuminuria | Moderate-to-High Risk or Established ASCVD | PVD | Retinopathy
Goal BP may be higher for Autonomic Neuropathy | Orthostatic Hypotension | Acute Coronary Syndrome | Frailty | Medication Intolerance
LIFESTYLE INTERVENTION
Decrease Sodium Intake | Diet (DASH, Mediterranean) | Physical Activity | Achieve Optimal Weight
ARB OR ACEi[c]
For initial SBP >150 mmHg and/or DBP >100 mmHg, consider starting dual therapy with an agent below
TITRATE MEDICATION DOSE OR ADD ON THERAPY EVERY 2-3 MONTHS TO REACH GOAL
THIAZIDE[d] | CALCIUM CHANNEL BLOCKER[e]
MRA[f] | COMBINED α-β BLOCKER[g] | β1 SELECTIVE BLOCKER[h]
ADDITIONAL ANTIHYPERTENSIVE AGENTS[k]: CENTRAL α2 AGONIST | PERIPHERAL α1-BLOCKER | HYDRALAZINE

[a]Screening for primary hyperaldosteronism is recommended in adults with hypertension. [b]For BP goals, consider person-specific characteristics: DKD, retinopathy, ASCVD, post-Mi, CHF, age, and race. [c]Rule out pregnancy. Use as first line for UACR >30 mg/g. ACEi and ARB should not be used concomitantly or with a direct renin inhibitor. Thiazide or CCB may also be appropriate as first line in absence of albuminuria. [d]Chlorthalidone, indapamide > hydrochlorothiazide. [e]Dihydropyridine (eg, amlodipine, nifedipine) unless other indication for non-dihydropyridine. [f]Steroidal MRAs spironolactone or eplerenone for resistant hypertension with >140/90 mmHg if already on 3 agents (ACEi/ARB, CCB, maximum-dose diuretic). Increase frequency of laboratory monitoring for combination of ACEi or ARB with MRA due to risk of hyperkalemia and AKI. Finerenone is a nonsteroidal MRA that is not indicated for hypertension but is recommended for individuals with CKD associated with T2D and eGFR ≥25 ml/min/1.73 m^2 and UACR ≥30 mg/g. [g]Carvedilol, labetalol, dilevalol. [h]Nebivolol, betaxolol. [k]Initiation of SGLT2i or GLP-1 RA also may mildly lower BP.

Abbreviations: **ACEi**, angiotensin-converting enzyme inhibitor; **AKI**, acute kidney injury; **ARB**, angiotensin II receptor blocker; **ASCVD**, atherosclerotic cardiovascular disease; **BP**, blood pressure; **CCB**, calcium channel blocker; **CHF**, congestive heart failure; **DASH**, Dietary Approaches to Stop Hypertension; **DBP**, diastolic blood pressure; **DKD**, diabetic kidney disease; **eGFR**, estimated glomerular filtration rate; **GLP-1 RA**, glucagon-like peptide-1 receptor agonist; **MI**, myocardial infarction; **MRA**, mineralocorticoid receptor antagonist; **PVD**, peripheral vascular disease; **SBP**, systolic blood pressure; **SGLT2i**, sodium glucose cotransporter-2 inhibitor; **UACR**, urine albumin-to-creatinine ratio

Algorithm Fig. 5. Atherosclerotic cardiovascular disease risk reduction algorithm: hypertension.

Comorbidities and complications must be managed for comprehensive care

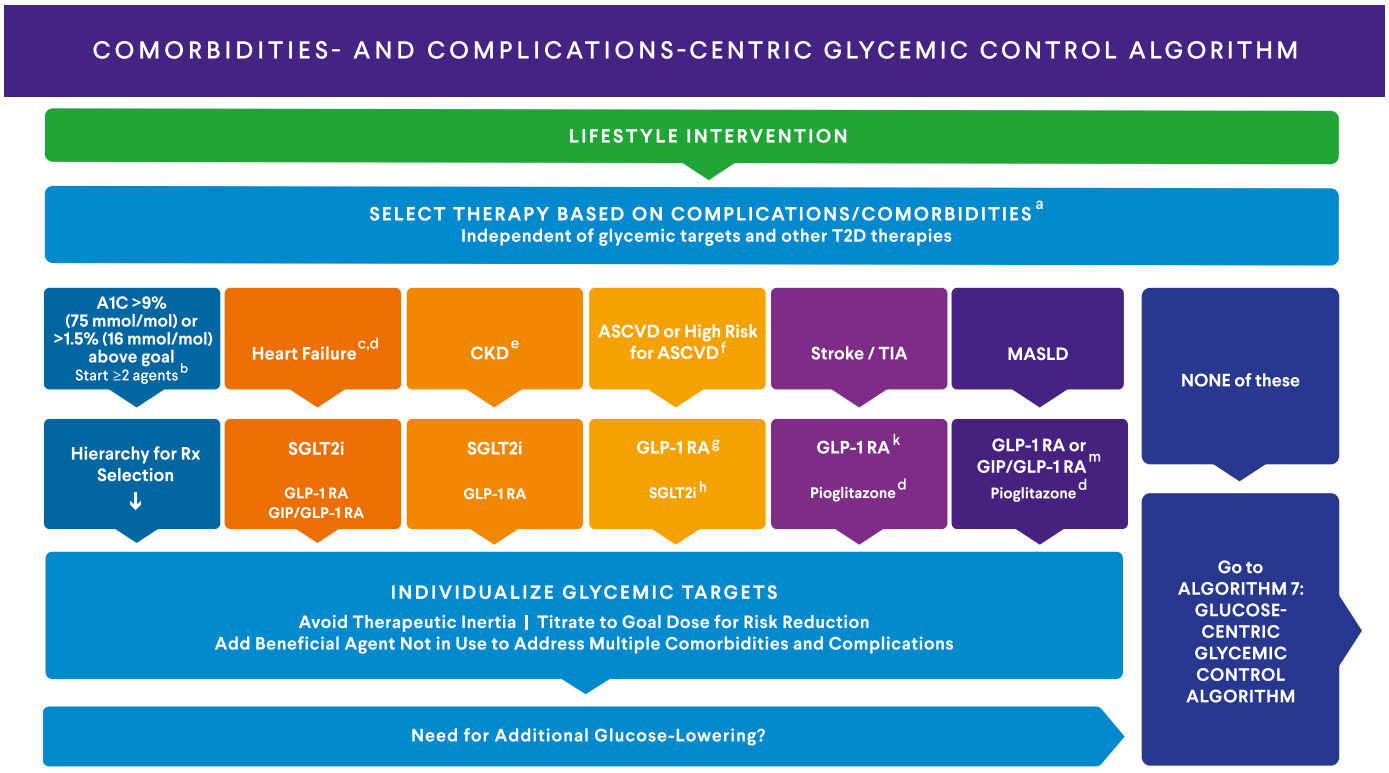
HTN and dyslipidemia are comorbidities associated with T2D that further increase the risk for complications including ASCVD, CKD, and retinopathy. Improvements in glycemic control must be accompanied by treatment of concomitant dyslipidemia (Algorithm Fig. 4) and HTN (Algorithm Fig. 5) for optimal outcomes. Comprehensive management of T2D requires a multidisciplinary approach, and appropriate specialist referrals should be made to address retinopathy, nephropathy, neuropathy, peripheral vascular disease, diabetic foot disease, and other associated complications and conditions. When present, additional components associated with ABCD also should be investigated and managed.[26]

Algorithm 2. Prediabetes Algorithm

Prediabetes is a cardiometabolic state resulting from failure of the pancreas to secrete enough insulin to compensate for insulin resistance, most often caused by overweight/obesity. Prediabetes continues to be defined by the presence of impaired fasting glucose (IFG) (100–125 mg/dL [5.6–6.9 mmol/L]) and/or impaired glucose tolerance (IGT) (140–199 mg/dL [7.8–11 mmol/L]) at 2 hours of an oral glucose tolerance test (OGTT) with ingestion of 75 g of glucose.[10] A1C values of 5.7% to 6.4% (39–47 mmol/mol) may indicate chronic hyperglycemia and the existence of prediabetes, but an OGTT is recommended to confirm diagnosis (Algorithm Fig. 2).[10] Metabolic syndrome using National Cholesterol Education Program Adult Treatment Panel III criteria is considered a prediabetes equivalent, so that adults meeting the definition of metabolic syndrome are also considered to be at high risk for developing DM.[69,70] There are ample data that prediabetes confers an increased risk for progression to T2D and ASCVD,[71-73] and the presence of both IFG and IGT during OGTT confers the highest risk for progression to T2D compared to IGT with normal fasting glucose.[74]

A key objective in the management of an individual with prediabetes and/or metabolic syndrome is to promote intentional weight loss, when appropriate and/or prevent weight gain to mitigate insulin resistance. The combination of prediabetes with overweight/obesity also should prompt clinicians to assess adults for additional complications of ABCD to guide clinical assessment and treatment.[26] In addition to actions intended to prevent or delay progression to overt T2D, attention should be given to treatment of ASCVD risk factors, HTN and dyslipidemia, and prevention of the development or progression of MASLD.

Lifestyle interventions that have been shown to reduce progression to T2D[75-77] and decrease the risk of ASCVD should be part of the strategy for all individuals with prediabetes independent of weight status. The prediabetes algorithm recommends medical nutrition therapy, with reduction of caloric intake to achieve weight loss in those with overweight or obesity, appropriately


COMORBIDITIES- AND COMPLICATIONS-CENTRIC GLYCEMIC CONTROL ALGORITHM
LIFESTYLE INTERVENTION
SELECT THERAPY BASED ON COMPLICATIONS/COMORBIDITIES [a]
Independent of glycemic targets and other T2D therapies
A1C >9% (75 mmol/mol) or >1.5% (16 mmol/mol) above goal
Start ≥2 agents [b]
Heart Failure [c,d]
CKD [e]
ASCVD or High Risk for ASCVD [f]
Stroke / TIA
MASLD
NONE of these
Hierarchy for Rx Selection
SGLT2i
GLP-1 RA
GIP/GLP-1 RA
SGLT2i
GLP-1 RA
GLP-1 RA [g]
SGLT2i [h]
GLP-1 RA [k]
Pioglitazone [d]
GLP-1 RA or GIP/GLP-1 RA [m]
Pioglitazone [d]
INDIVIDUALIZE GLYCEMIC TARGETS
Avoid Therapeutic Inertia | Titrate to Goal Dose for Risk Reduction
Add Beneficial Agent Not in Use to Address Multiple Comorbidities and Complications
Need for Additional Glucose-Lowering?
Go to ALGORITHM 7: GLUCOSE-CENTRIC GLYCEMIC CONTROL ALGORITHM

[a]CVOTs included metformin as baseline therapy. [b]For SEVERE HYPERGLYCEMIA (A1C >10% [>86 mmol/mol] and/or glucose >300 mg/dL [16.7 mmol/L]) with symptoms, strongly consider basal insulin (Go to ALGORITHM 8: INITIATING AND TITRATING INSULIN). Avoid use of GLP-1 RA or GIP/GLP-1 RA alone in severe hyperglycemia. These agents require titration over weeks delaying glycemic control.[c]Use SGLT2i with proven benefit (dapagliflozin, empagliflozin). Semaglutide/tirzepatide have potential benefit in obesity-related HFpEF. [d]TZDs are contraindicated in NYHA Class III/IV HF. Start at 15 mg, and balance benefits vs risks of weight gain. Allow >4 weeks at each dose before titration. [e]CKD: Use SGLT2i with proven benefit (canagliflozin, dapagliflozin, empagliflozin) or GLP-1 RA (semaglutide injection). [f]High risk for ASCVD: age ≥55 AND albuminuria or proteinuria, hypertension and LV hypertrophy, LV systolic or diastolic dysfunction, ankle-brachial index <0.9. [g]GLP-1 RA: oral or subcutaneous semaglutide, liraglutide, or dulaglutide. [h]SGLT2i: canagliflozin, empagliflozin, or dapagliflozin. [k]Stroke: semaglutide subcutaneous or dulaglutide. [m]MASLD: semaglutide or tirzepatide.

Abbreviations: **A1C**, hemoglobin A1c; **ASCVD**, atherosclerotic cardiovascular disease; **CKD**, chronic kidney disease; **CVOT**, cardiovascular outcomes trial; **eGFR**, estimated glomerular filtration rate; **GIP**, glucose-dependent insulinotropic polypeptide; **GLP-1 RA**, glucagon-like peptide-1 receptor agonist; **HF**, Heart Failure; **HFpEF**, heart failure with preserved ejection fraction; **LV**, left ventricular; **MASLD**, metabolic dysfunction-associated steatotic liver disease; **NYHA**, New York Heart Association; **Rx**, prescription; **SGLT2i**, sodium glucose cotransporter 2 inhibitor; **T2D**, type 2 diabetes; **TIA**, transient ischemic attack; **TZD**, thiazolidinedione; **UACR**, urine albumin-creatinine ratio

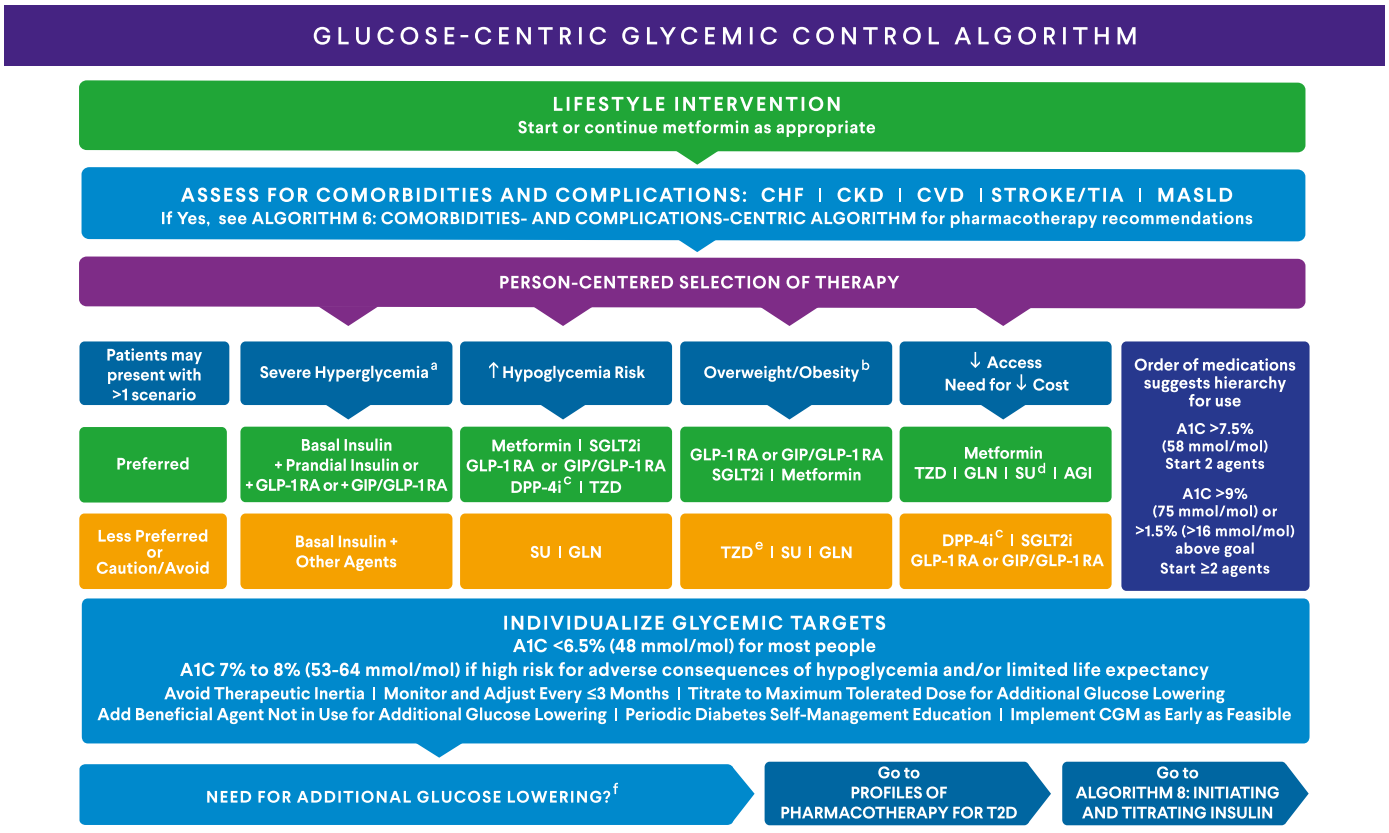
Algorithm Fig. 6. Comorbidities- and complications-centric glycemic control algorithm.

prescribed physical activity, avoidance of tobacco products, and adequate sleep quantity and quality. Dietary interventions should involve a healthy meal plan, such as the Mediterranean[78,79] or Dietary Approaches to Stop Hypertension (DASH) diet.[80,81] Other diets, including low-fat, low-carbohydrate, vegetarian, and vegan diets, can also be considered. Regular physical activity through a combination of aerobic and resistance exercises to achieve 150 minutes per week of moderately intense aerobic exercise over 3 to 5 sessions and resistance exercise consisting of single-set repetitions targeting the major muscle groups 2 to 3 times per week should be added.[82-86] Nonexercise active leisure activities should be encouraged to reduce sedentary behavior. Behavioral health should be incorporated for optimal outcomes.

Weight loss is highly effective in preventing or delaying the progression of prediabetes to T2D. Lifestyle interventions, discussed above, to promote weight loss are essential, but the addition of weight-loss pharmacotherapies or bariatric procedures may need to be considered depending on person-specific characteristics, including stage of obesity.[11] Data have shown that weight reduction of 7% to 10% is an important threshold in adults with overweight/obesity, as this degree of weight loss has been demonstrated to be effective in preventing or delaying progression to T2D.[75,87] Obesity medications shown to have efficacy to achieve at least 7% to 10% weight loss include semaglutide subcutaneous injection (≥2.4 mg), tirzepatide, liraglutide (3 mg), and phentermine/topiramate-extended release (ER) 7.5/46 mg daily or higher.[87-93]

The presence of additional complications of ABCD also may influence the choice of pharmacotherapy. Semaglutide 2.4 mg has been approved by the U.S. Food and Drug Administration (FDA) for use without T2D if body mass index (BMI) is ≥30.0 kg/m^2 or if BMI ≥27.0 kg/m^2 with ≥1 weight-related condition (eg, HTN, dyslipidemia) and, more recently, with established ASCVD[93] or noncirrhotic MASH with moderate to advanced liver fibrosis.[20] Tirzepatide has been approved by the FDA as a treatment for moderate to severe OSA in individuals with obesity, based on the outcomes from the SURMOUNT-OSA trial, in which nearly two-thirds of participants also had prediabetes.[15] These approved agents should be the first-line choice for weight loss when these particular comorbidities coexist. Other approved medications for the treatment of adults with obesity (naltrexone-ER/bupropion-ER, short-term phentermine, or orlistat) can be considered if the above medications are not tolerated or are not accessible (see Profiles of Pharmacotherapy for Obesity Table in Algorithm Fig. 10).

Additional medical devices have regulatory approval as nonpharmacologic weight loss interventions. Hydrogel capsules (oral), containing cellulose and citric acid and taken 20 to 30 minutes prior to a meal, are an option for nonpregnant adults with a BMI 25.0 kg/m^2 to 40.0 kg/m^2. A majority of participants (59%) in a placebo-controlled trial, including individuals with prediabetes


GLUCOSE-CENTRIC GLYCEMIC CONTROL ALGORITHM
LIFESTYLE INTERVENTION
Start or continue metformin as appropriate
ASSESS FOR COMORBIDITIES AND COMPLICATIONS: CHF | CKD | CVD | STROKE/TIA | MASLD
If Yes, see ALGORITHM 6: COMORBIDITIES- AND COMPLICATIONS-CENTRIC ALGORITHM for pharmacotherapy recommendations
PERSON-CENTERED SELECTION OF THERAPY
Patients may present with >1 scenario
Severe Hyperglycemia [a]
↑ Hypoglycemia Risk
Overweight/Obesity [b]
↓ Access Need for ↓ Cost
Order of medications suggests hierarchy for use
A1C >7.5% (58 mmol/mol) Start 2 agents
A1C >9% (75 mmol/mol) or >1.5% (>16 mmol/mol) above goal Start ≥2 agents
Preferred
Basal Insulin + Prandial Insulin or + GLP-1 RA or + GIP/GLP-1 RA
Metformin | SGLT2i GLP-1 RA or GIP/GLP-1 RA DPP-4i [c] | TZD
GLP-1 RA or GIP/GLP-1 RA SGLT2i | Metformin
Metformin TZD | GLN | SU [d] | AGI
Less Preferred or Caution/Avoid
Basal Insulin + Other Agents
SU | GLN
TZD [e] | SU | GLN
DPP-4i [c] | SGLT2i GLP-1 RA or GIP/GLP-1 RA
INDIVIDUALIZE GLYCEMIC TARGETS
A1C <6.5% (48 mmol/mol) for most people
A1C 7% to 8% (53-64 mmol/mol) if high risk for adverse consequences of hypoglycemia and/or limited life expectancy
Avoid Therapeutic Inertia | Monitor and Adjust Every ≤3 Months | Titrate to Maximum Tolerated Dose for Additional Glucose Lowering
Add Beneficial Agent Not in Use for Additional Glucose Lowering | Periodic Diabetes Self-Management Education | Implement CGM as Early as Feasible
NEED FOR ADDITIONAL GLUCOSE LOWERING? [f]
Go to PROFILES OF PHARMACOTHERAPY FOR T2D
Go to ALGORITHM 8: INITIATING AND TITRATING INSULIN

[a]For SEVERE HYPERGLYCEMIA (A1C >10% [>86 mmol/mol] and/or glucose >300 mg/dL [16.7 mmol/L] with symptoms), strongly consider basal insulin (Go to ALGORITHM 8: INITATING AND TITRATING INSULIN). Avoid use of GLP-1 RA or GIP/GLP-1 RA alone in severe hyperglycemia. These agents require titration over weeks which can delay glycemic control. After glucose toxicity is resolved, reassess medical therapy and consider other agents. [b]See **AACE Algorithm for the Treatment of Obesity/Adiposity-Based Chronic Disease-2025 Update**. [c]DPP-4i and GLP-1 RA or GIP/GLP-1 RA should not be combined. [d]SUs may be inappropriate in older adults due to risk of hypoglycemia. [e]TZDs can cause increased weight partially attributable to fluid retention. [f]If despite appropriate therapy and adherence, glucose levels remain above target, also reconsider ALGORITHM 3: DIABETES CLASSIFICATION.

Abbreviations: **A1C**, hemoglobin A1C; **AGI**, alpha-glucosidase inhibitor; **CGM**, continuous glucose monitoring; **CHF**, congestive heart failure; **CKD**, chronic kidney disease; **CVD**, cardiovascular disease; **DPP-4i**, dipeptidyl peptidase 4 inhibitor; **GIP**, glucose-dependent insulinotropic polypeptide; **GLN**, glinide; **GLP-1 RA**, glucagon-like peptide 1 receptor agonist; **MASLD**, metabolic dysfunction-associated steatotic liver disease; **SGLT2i**, sodium glucose transporter 2 inhibitor; **SU**, sulfonylurea; **TIA**, transient ischemic attack; **T2D**, type 2 diabetes; **TZD**, thiazoladinedione

Algorithm Fig. 7. Glucose-centric glycemic control algorithm.

and T2D, achieved 5% weight loss with 27% achieving ≥10% weight loss (vs 15% on placebo).[94] Additional devices that have regulatory approval by the FDA for the treatment of adults with obesity, but not T2D, include intragastric balloons, transpyloric shuttle, and gastric aspiration.[95-97] Metabolic (bariatric) surgery procedures also are another option in adults with prediabetes and BMI ≥35.0 kg/m^2.[98,99]

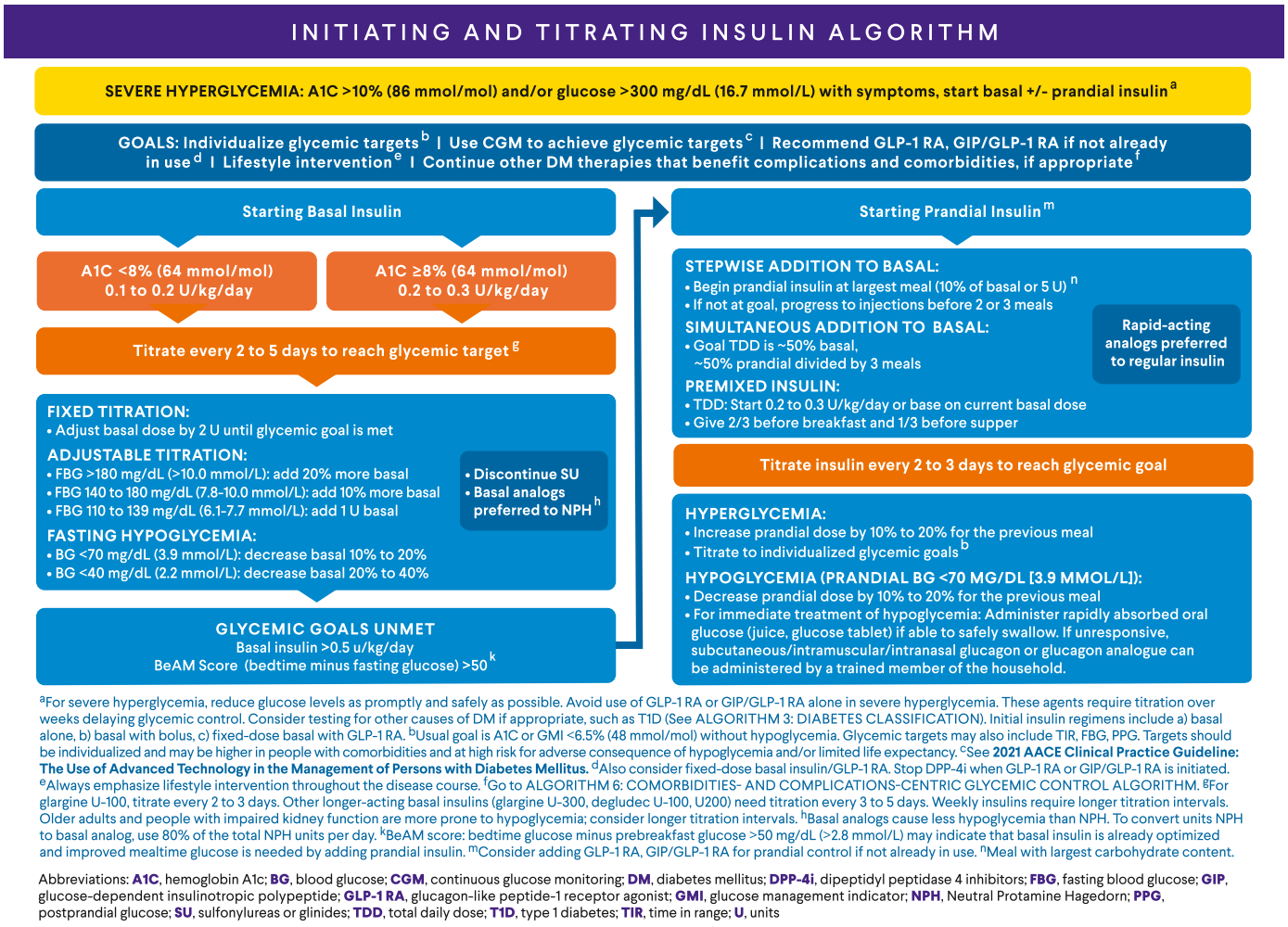
Although there are currently no antihyperglycemic drugs with explicit regulatory approval to prevent progression of prediabetes to T2D, metformin, pioglitazone, and acarbose have evidence of efficacy in clinical trials.[75,100,101]

If there is an absence of overweight/obesity, the possibility of other etiologies of dysglycemia beyond insulin resistance should be considered for an adult with prediabetes, including early presentation of type 1 diabetes (T1D) or latent autoimmune diabetes in adults (LADA) which could merit screening for autoantibodies to β-cell antigens. Autoantibody screening may also be considered in individuals with a personal or family history of autoimmune disease, including T1D, regardless of the presence of overweight or obesity (see Algorithm Fig. 3 for DM diagnosis and classification). Detection of early-stage T1D provides the opportunity for treatment with approved agents or referral to clinical trials (https://www.trialnet.org) to delay progression to overt T1D.[102]

Despite the recommended interventions discussed above, some adults with prediabetes will progress to T2D. For further guidance on adding antihyperglycemic pharmacotherapy, see sections on the Comorbidities- and Complications-Centric Glycemic Control Algorithm (Algorithm Fig. 6) and the Glucose-Centric Glycemic Control Algorithm (Algorithm Fig. 7).

Algorithm 3. Diabetes Classification Algorithm

Although T2D is the most prevalent form of DM, it is important to ensure the accurate diagnostic classification of DM. Overweight/obesity and insulin resistance are prevalent and may mislead clinicians to make assumptions that lead to a default diagnosis of T2D.[103,104] An incorrect diagnosis is unfortunately common. In a report from the United Kingdom Diabetes Alliance for Research in England (DARE) cohort, nearly 40% of adults over 30 years of age who met the criteria for T1D were treated as though they had T2D and did not receive insulin at the time of diagnosis.[105] Incorrect classification of an individual with T1D can have serious sequelae, including diabetic ketoacidosis (DKA).[102,106] It also is important to consider secondary causes of DM, when clinically indicated, which can inform additional investigations and specific management strategies. To ensure a correct treatment approach, this algorithm reviews steps to confirm the etiology of the DM. Algorithm Fig. 3 may be applied to new diagnoses of DM or used at any point after diagnosis to ensure the correct classification of DM, which can impact management. Given concerns of misdiagnosis or delayed


INITIATING AND TITRATING INSULIN ALGORITHM
SEVERE HYPERGLYCEMIA: A1C >10% (86 mmol/mol) and/or glucose >300 mg/dL (16.7 mmol/L) with symptoms, start basal +/- prandial insulin [a]
GOALS: Individualize glycemic targets [b] | Use CGM to achieve glycemic targets [c] | Recommend GLP-1 RA, GIP/GLP-1 RA if not already in use [d] | Lifestyle intervention [e] | Continue other DM therapies that benefit complications and comorbidities, if appropriate [f]
Starting Basal Insulin
A1C <8% (64 mmol/mol) 0.1 to 0.2 U/kg/day
A1C ≥8% (64 mmol/mol) 0.2 to 0.3 U/kg/day
Titrate every 2 to 5 days to reach glycemic target [g]
FIXED TITRATION:
• Adjust basal dose by 2 U until glycemic goal is met
ADJUSTABLE TITRATION:
• FBG >180 mg/dL (>10.0 mmol/L): add 20% more basal
• FBG 140 to 180 mg/dL (7.8-10.0 mmol/L): add 10% more basal
• FBG 110 to 139 mg/dL (6.1-7.7 mmol/L): add 1 U basal
FASTING HYPOGLYCEMIA:
• BG <70 mg/dL (3.9 mmol/L): decrease basal 10% to 20%
• BG <40 mg/dL (2.2 mmol/L): decrease basal 20% to 40%
• Discontinue SU
• Basal analogs preferred to NPH [h]
GLYCEMIC GOALS UNMET
Basal insulin >0.5 u/kg/day
BeAM Score (bedtime minus fasting glucose) >50 [k]
Starting Prandial Insulin [m]
STEPWISE ADDITION TO BASAL:
• Begin prandial insulin at largest meal (10% of basal or 5 U) [n]
• If not at goal, progress to injections before 2 or 3 meals
SIMULTANEOUS ADDITION TO BASAL:
• Goal TDD is ~50% basal, ~50% prandial divided by 3 meals
PREMIXED INSULIN:
• TDD: Start 0.2 to 0.3 U/kg/day or base on current basal dose
• Give 2/3 before breakfast and 1/3 before supper
Rapid-acting analogs preferred to regular insulin
Titrate insulin every 2 to 3 days to reach glycemic goal
HYPERGLYCEMIA:
• Increase prandial dose by 10% to 20% for the previous meal
• Titrate to individualized glycemic goals [b]
HYPOGLYCEMIA (PRANDIAL BG <70 MG/DL [3.9 MMOL/L]):
• Decrease prandial dose by 10% to 20% for the previous meal
• For immediate treatment of hypoglycemia: Administer rapidly absorbed oral glucose (juice, glucose tablet) if able to safely swallow. If unresponsive, subcutaneous/intramuscular/intranasal glucagon or glucagon analogue can be administered by a trained member of the household.

[a]For severe hyperglycemia, reduce glucose levels as promptly and safely as possible. Avoid use of GLP-1 RA or GIP/GLP-1 RA alone in severe hyperglycemia. These agents require titration over weeks delaying glycemic control. Consider testing for other causes of DM if appropriate, such as T1D (See ALGORITHM 3: DIABETES CLASSIFICATION). Initial insulin regimens include a) basal alone, b) basal with bolus, c) fixed-dose basal with GLP-1 RA. [b]Usual goal is A1C or GMI <6.5% (48 mmol/mol) without hypoglycemia. Glycemic targets may also include TIR, FBG, PPG. Targets should be individualized and may be higher in people with comorbidities and at high risk for adverse consequence of hypoglycemia and/or limited life expectancy. [c]See **2021 AACE Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons with Diabetes Mellitus.** [d]Also consider fixed-dose basal insulin/GLP-1 RA. Stop DPP-4i when GLP-1 RA or GIP/GLP-1 RA is initiated. [e]Always emphasize lifestyle intervention throughout the disease course. [f]Go to ALGORITHM 6: COMORBIDITIES- AND COMPLICATIONS-CENTRIC GLYCEMIC CONTROL ALGORITHM. [g]For glargine U-100, titrate every 2 to 3 days. Other longer-acting basal insulins (glargine U-300, degludec U-100, U200) need titration every 3 to 5 days. Weekly insulins require longer titration intervals. Older adults and people with impaired kidney function are more prone to hypoglycemia; consider longer titration intervals. [h]Basal analogs cause less hypoglycemia than NPH. To convert units NPH to basal analog, use 80% of the total NPH units per day. [k]BeAM score: bedtime glucose minus prebreakfast glucose >50 mg/dL (>2.8 mmol/L) may indicate that basal insulin is already optimized and improved mealtime glucose is needed by adding prandial insulin. [m]Consider adding GLP-1 RA, GIP/GLP-1 RA for prandial control if not already in use. [n]Meal with largest carbohydrate content.

Abbreviations: **A1C**, hemoglobin A1c; **BG**, blood glucose; **CGM**, continuous glucose monitoring; **DM**, diabetes mellitus; **DPP-4i**, dipeptidyl peptidase 4 inhibitors; **FBG**, fasting blood glucose; **GIP**, glucose-dependent insulinotropic polypeptide; **GLP-1 RA**, glucagon-like peptide-1 receptor agonist; **GMI**, glucose management indicator; **NPH**, Neutral Protamine Hagedorn; **PPG**, postprandial glucose; **SU**, sulfonylureas or glinides; **TDD**, total daily dose; **T1D**, type 1 diabetes; **TIR**, time in range; **U**, units

Algorithm Fig. 8. Initiating and titrating insulin algorithm.

diagnosis, T2D should not be assumed automatically, even in the presence of a preexisting label of T2D, and reassessment should be considered if appropriate as outlined below.

Step 1. Confirm DM Using Diagnostic Criteria

DM is defined by the presence of FPG ≥126 mg/dL (>7 mmol/L), 2-hour 75-g OGTT ≥200 mg/dL (>11.1 mmol/L), A1C ≥6.5% (≥48 mmol/mol), or random glucose ≥200 mg/dL (>11.1 mmol/L) with symptoms of hyperglycemia (eg, polyuria, polydipsia, weight loss).[10,107] In the absence of symptoms of hyperglycemia, a different confirmatory test performed at the same time or the same or different test performed at another time, but in a timely fashion, is recommended.[107] In cases where 2 different test results are discordant, another confirmatory test may be required, with a recommendation to repeat the test that was abnormal at the initial assessment.[107]

Step 2. Check for T2D Phenotype

Once DM diagnostic criteria are met, the next step involves a review of the history, physical examination, and laboratory results to assess the presence or absence of a T2D phenotype. Factors in an individual's history that support a diagnosis of T2D include the presence of overweight (BMI 25.0 kg/m^2–29.9 kg/m^2) or obesity (BMI ≥30.0 kg/m^2 or greater) or history of weight gain.[11] BMI cutoffs should be adjusted for race/ethnicity if appropriate, particularly for adults of Asian descent where BMI ≥23.0 kg/m^2 (overweight) and ≥25.0 kg/m^2 (obese) may better reflect cardiometabolic risk.[108-111] A cautionary note is required regarding sole reliance on overweight or obesity to confirm T2D, as a proportion of adults with evolving T1D also can have a BMI ≥25.0 kg/m^2. In the DARE cohort, 59% of individuals with late-onset T1D (>30 years of age) had a BMI ≥25.0 kg/m^2.[105] Conversely, a proportion of adults with T2D can also have low or normal BMI, reported as approximately 12% from a U.S. database, which is further influenced by ethnic background.[112,113] Other clinical findings supportive of T2D include a personal history of gestational DM, family history of T2D, and physical exam findings consistent with insulin resistance (eg, acanthosis). For confirmed T2D, the clinician can proceed to the Comorbidities- and Complications-Centric (Algorithm Fig. 6) and Glucose-Centric (Algorithm Fig. 7) algorithms.

Step 3. Are Other Types of Diabetes Suspected?

Individuals who do not clearly match the expected presentation of T2D should undergo further evaluation to establish whether another type of DM may be present. Adults who received a diagnosis of T2D and, despite adherence to optimal noninsulin

PROFILES OF PHARMACOTHERAPY FOR TYPE 2 DIABETES

		METFORMIN	GLP-1 RA	GIP/GLP-1 RA	SGLT2i	TZD	DPP-4i	SU	GLN	AGI	INSULIN
EFFICACY FOR GLUCOSE LOWERING[a]		++	++/+++	++/++++	+/++	++	+/++	++/+++	+/++	+/++	++++
ASCVD	MACE		Benefit[b]	Benefit[b]	Benefit[c]						
	STROKE		Benefit[d]	Benefit[d]	Benefit[c]	Benefit					
CHF[e]			Potential Benefit[e]	Potential Benefit[e]	Benefit	Contraindicated NYHA Class III/IV[f]	Saxagliptin Alogliptin[g]				Moderate
CKD			Benefit[d]	Benefit	Benefit						
RENAL IMPAIRMENT		Decrease Dose for eGFR 30 to 45[h]	Exenatide for eGFR 30 to 45[k]		↓Glycemic Efficacy at Lower eGFR		Adjust Dose[n]	↑ Hypoglycemia Risk	↑ Hypoglycemia Risk	Contraindicated eGFR<25 or Serum Cr >2 mg/dL	↑ Hypoglycemia Risk
		Contraindicated for eGFR <30[h]	Exenatide Contraindicated for eGFR <30		Check Drug-Specific eGFR Thresholds[m]						
HYPOGLYCEMIA RISK								Moderate to High[o]	Low to Moderate		Moderate to High
WEIGHT		Slight Loss	Loss	Loss	Mild Loss	Gain[f]		Gain			Gain
MASLD[p]	HEPATIC STEATOSIS		Benefit[q]	Potential Benefit	Potential Benefit	Potential Benefit					Potential Benefit
	MASH		Benefit[q]	Potential Benefit		Potential Benefit					
	FIBROSIS PROGRESSION		Benefit[q]	Potential Benefit		Potential Benefit					
	FIBROSIS REGRESSION		Benefit[q]	Potential Benefit	Potential Benefit	Potential Benefit					
GI ADVERSE SYMPTOMS		Mild to Moderate	Moderate[r]	Moderate[r]						Moderate	
OTHER CONSIDERATIONS			MTC/MEN2	OSA	GU Infections Euglycemic DKA[s] ↑ Fracture Risk[t]	↑ Fracture Risk[t] Bladder Cancer	Rare Arthralgias/ Myalgias				
				MTC/MEN2							
ACCESS/COST		$	$$$	$$$	$$$	$	$-$$	$	$-$$	$-$$	$ - $$$

Benefits | Use with caution | Contraindicated | Neutral, not studied, or insufficient evidence

[a]Each "+" approximates 0.5% A1C lowering. [b]GLP-1 RA MACE benefits with liraglutide, dulaglutide, semaglutide (oral or subcutaneous). Tirzepatide is non-inferior to dulaglutide for MACE. [c]SGLT2i MACE benefits and potential hemorrhagic stroke benefit with empagliflozin, canagliflozin. [d]Stroke and CKD benefits with dulaglutide, semaglutide. Tirzepatide is non-inferior to dulaglutide for stroke. [e]Obesity-related HFpEF. [f]TZDs increase fluid retention and edema and are contraindicated in CHF NYHA Class III/IV. [g]Increased CHF hospitalization risk with saxagliptin and alogliptin. [h]Contraindicated in CKD4 (eGFR <30 ml/min/1.73 m^2). For CKD3b (eGFR 30 to <45 mL/min/1.73 m^2), do not initiate or initiate with caution to maximum 500 mg twice per day. Hold for acute kidney injury or intravenous contrast. [k]Exenatide CKD3b (eGFR 30 to <45 mL/minute/1.73 m^2) use not recommended or monitor closely. [m]The eGFR thresholds for initiation and/or continuation in CKD vary among SGLT2i. Check drug-specific eGFR thresholds. Not for use for eGFR <20 ml/min/1.73 m^2. [n]Only linagliptin does not require adjustment. [o]Single-agent risks of hypoglycemia may be low but increases when combined with other agents or with CKD (glyburide > glipizide/glimepiride/gliclazide). [p]Adapted from Cusi et al. 2025. [q]Shown for semaglutide. [r]Use slow titration, portion control, and reduce to prior tolerated dose if disruptive. [s]Precipitants include significant concurrent illness, surgery, inappropriate/rapid insulin dose reduction, and fasting. [t]Reported with canagliflozin, dapagliflozin, and pioglitazone.

Abbreviations: **A1C**, hemoglobin A1c; **AGI**, alpha-glucosidase inhibitor; **ASCVD**, atherosclerotic cardiovascular disease; **CHF**, congestive heart failure; **CKD**, chronic kidney disease; **Cr**, creatinine; **DKA**, diabetic ketoacidosis; **DPP-4i**, dipeptidyl peptidase-4 inhibitor; **eGFR**, estimated glomerular filtration rate; **GI**, gastrointestinal; **GIP**, glucose-dependent insulinotropic polypeptide; **GLN**, glinide or meglitinide; **GLP-1 RA**, glucagon-like peptide-1 receptor agonist; **GU**, genitourinary; **HFpEF**, heart failure with preserved ejection fraction; **MACE**, major adverse cardiovascular events; **MASH**, metabolic dysfunction-associated steatohepatitis; **MASLD**, metabolic-associated steatotic liver disease; **MEN2**, multiple endocrine neoplasia type 2; **MET**, metformin; **MTC**, medullary thyroid carcinoma; **NYHA**, New York Heart Association; **SGLT2i**, sodium glucose cotransporter 2 inhibitor; **SU**, sulfonylurea; **TZD**, thiazolidinedione

Algorithm Fig. 9. Profiles of pharmacotherapy for type 2 diabetes.

pharmacotherapy, remain uncontrolled or rapidly progress to exogenous insulin dependence (<3 years from diagnosis) may require assessment for other types or causes of DM.[114] Other examples include those who easily develop ketosis with SGLT2i, those at either end of the spectrum of insulin resistance (total daily insulin dose of <0.5 u/kg or >2 u/kg), or those without the expected clinical response to metformin or insulin secretagogues.

Step 4. Assess for T1D

A common misconception is that T1D is only diagnosed in childhood. In actuality, a large proportion of individuals with T1D report diagnosis as an adult, with 37% of individuals with T1D diagnosed over the age of 30 years.[115] In addition, the majority of incident T1D cases are in adults.[114] To further confound accurate classification,[114-116] LADA refers to a subtype of autoimmune diabetes with a more gradual onset, milder symptoms, and a delayed progression to insulin dependence with progressive loss of C-peptide over time.[117-119]

It is important for clinicians to be mindful of the high rates of misclassification of T1D in adults and to have a low suspicion to evaluate for T1D in the presence of risk factors or clinical criteria suggesting the potential for T1D. Family history of T1D is a strong risk factor, with a 15-fold higher rate of T1D in first-degree relatives compared with the general population.[120] The presence of a lean body habitus and absence of examination findings of insulin resistance may prompt an evaluation for T1D, although people of all types of body habitus can develop T1D.[105] A history of DKA should trigger an assessment for T1D, although not all people with DKA have T1D. Some individuals with T2D may develop DKA in association with SGLT2i or with an entity that has been termed ketosis-prone DM, which was first described in people of African descent but is now known to affect individuals from multiple and diverse racial backgrounds.[121-123] A personal or family history of autoimmune disease(s) (eg, Hashimoto, Graves', Addison, or celiac disease) is also associated with T1D and should increase suspicion for autoimmune DM.[114,120]

To evaluate for T1D, laboratory testing should be ordered to assess for T1D autoantibodies: glutamic acid decarboxylase autoantibody (GAD65 or GADA), insulinoma antigen-2 autoantibody, zinc transporter 8 antibody (Ab), and insulin autoantibody.[102] Insulin autoantibody is more commonly elevated in children but can also be positive with a history of insulin exposure,[124,125] while GAD65 is the most prevalent autoantibody in adults,[114,117] including for LADA. Notably, if T1D Abs are checked while on a corticosteroid or immunosuppressants, a positive result could be masked. Approximately 10% of individuals with T1D are Ab negative, which may add complexity to making the diagnosis.[126]

Another biomarker that can be of clinical value in assessing for T1D is C-peptide, as it is coupled to endogenous insulin production.[125,127] It is important to emphasize that there can be variability among C-peptide assays and further standardization is

PROFILES OF PHARMACOTHERAPY FOR OBESITY

	TIRZEPATIDE	SEMAGLUTIDE	LIRAGLUTIDE	PHENTERMINE-TOPIRAMATE ER	NALTREXONE ER/ BUPROPRION ER	ORLISTAT	PHENTERMINE[a]
CLASS	GIP/GLP-1 RA	GLP-1 RA	GLP-1 RA	Sympathomimetic Amine/Gabaminergic	Opioid-Receptor Antagonist/NDRI	GI Lipase Inhibitor	Sympathomimetic
WEIGHT LOSS[b]	13% to 20% 10% to 12% (T2D)	12% to 15% 8% to 11% (T2D)	5% to 6% 3% to 4% (T2D)	8% to 10% 4% to 7% (T2D)	4% to 5% 3% to 4% (T2D)	3% to 4% 3% (T2D)	3% to 5%
A1C REDUCTION WITH T2D	1.9% to 2.5%	1.4% to 2.1% 1.2% (Oral)	0.8% to 1.9%	0.4%	0.5% to 0.6%	0.6%	Not Available
MECHANISM	↓ Appetite ↑ Satiation/Satiety Delayed Gastric Emptying	↓ Appetite ↑ Satiation/Satiety Delayed Gastric Emptying	↓ Appetite ↑ Satiation/Satiety Delayed Gastric Emptying	↓ Appetite ↑ Satiety	↓ Cravings ↓ Appetite	↓ Fat Absorption	↓ Appetite
DELIVERY	Weekly SQ Injection	Weekly SQ Injection	Daily SQ Injection	Oral	Oral	Oral	Oral
DOSE (MIN - MAX)	2.5 mg to 15 mg Weekly	0.25 mg to 2.4 mg Weekly	0.6 mg to 3 mg Daily	3.75 mg/23 mg to 15 mg/92 mg Daily	8 mg/90 mg to 16 mg/180 mg Twice Daily	60 mg to 120 mg 3x Daily	15 mg to 37.5 mg Daily
DOSE TITRATION	↑ 2.5 mg Weekly, Every 4 Weeks	↑ 0.5, 1, 1.7, and 2.4 mg Weekly, Every 4 Weeks (Obesity) ↑ 0.5, 1, and 2 mg Weekly, Every 4 Weeks (T2D)	↑ 0.6 mg/kg Weekly	↑ to 7.5 mg/46 mg Daily	↑ One Tablet per Week	↓ 60 mg if 120 mg Not Tolerated	Dose Titration as per Needs
KEY ADVERSE EFFECTS	Nausea/Vomiting Diarrhea Constipation Dyspepsia Abdominal Pain Pancreatitis Headache Fatigue Hypoglycemia	Nausea/Vomiting Diarrhea Constipation Dyspepsia Abdominal Pain Pancreatitis Gallbladder Disease Headache Acute Kidney Injury Hypoglycemia	Nausea/Vomiting Diarrhea Constipation Dyspepsia Abdominal Pain Pancreatitis Gallbladder Disease Headache Acute Kidney Injury Hypoglycemia	Paresthesia Xerostomia Headache Dizziness Insomnia Changes in Taste Constipation Nausea Tachycardia	Nausea/Vomiting Constipation Headache Dizziness Suicidality Xerostomia Hypertension Insomnia	Oily Spotting Fecal Urgency Fatty/Oily Stool Fecal Incontinence Fat-Soluble Vitamin Deficiencies (ADEK)	Palpitations Tachycardia Hypertension Restlessness Dizziness Insomnia Headache Pulmonary HTN Dependency
CAUTIONS	Pancreatitis Hx Severe GI Disease & Gastroparesis Renal Impairment Diabetic Retinopathy Perioperative Aspiration Childbearing Women	Pancreatitis Hx Severe GI Disease & Gastroparesis Renal Impairment Diabetic Retinopathy Perioperative Aspiration Childbearing Women Nonarteritic Anterior Ischemic Optic Neuropathy	Pancreatitis Hx Severe GI Disease & Gastroparesis Renal Impairment Diabetic Retinopathy Perioperative Aspiration Childbearing Women	Childbearing Women Embryo-Fetal Toxicity Depression Suicidality Mood and Sleep Disorders Cognitive Impairment Metabolic Acidosis Renal Calculi	Childbearing Women Angle-Closure Glaucoma Hypoglycemia Drug Abuse Hx Seizure Risk Bipolar Disorder Hepatic Impairment Renal Impairment	Hyperoxaluria Hx Kidney Stones (Calcium Oxalate) Anorexia Nervosa Bulimia Hx Childbearing Women	Elderly Hypertension Seizures CrCl <30
CONTRAINDICATIONS[c]	Personal or Family Hx of MTC or MEN2	Personal or Family Hx of MTC or MEN2	Personal or Family Hx of MTC or MEN2	Glaucoma Hyperthyroidism Agitation MAOI Within 14 Days ASCVD Drug Abuse Hx Suicidality	MAOI Within 14 Days Eating Disorders Chronic Opioid Use Abrupt Discontinuation of Alcohol and Certain Drugs[d]	Chronic Malabsorption Cholestasis	MAOI Within 14 Days ASCVD Glaucoma Drug Abuse Hx
ACCESS/COST	$$$	$$$	$$$	$$	$$	$$	$

[a]Approved for short term ≤3 months. 15 mg / 30 mg / 37.5 mg phentermine hydrochloride = 12 mg / 24 mg / 30 mg phentermine resin. [b]Approximate placebo-subtracted percentages with 52 to 72 weeks of therapy except phentermine (12 weeks). [c]All agents are contraindicated in pregnancy/breastfeeding. [d]Benzodiazepines, barbiturates, and antiepileptic drugs.

Abbreviations: **A1C**, hemoglobin A1c; **ASCVD**, atherosclerotic cardiovascular disease; **CrCl**, creatinine clearance; **CV**, cardiovascular; **CVD**, cardiovascular disease; **DA**, dopamine; **ER**, extended release; **GI**, gastrointestinal; **GIP**, glucose-dependent insulinotropic polypeptide; **GLP-1 RA**, glucagon-like peptide-1 receptor agonist; **HTN**, hypertension; **Hx**, history; **MAOI**, monoamine oxidase inhibitor; **MEN2**, multiple endocrine neoplasia, type 2; **MTC**, medullary thyroid cancer; **NDRI**, norepinephrine and dopamine reuptake inhibitor; **SQ**, subcutaneous; **T2D**, type 2 diabetes

Algorithm Fig. 10. Profiles of pharmacotherapy for obesity.

needed.[128] The diagnostic use of C-peptide levels has been studied in the context of mixed-meal and glucagon stimulation testing,[128,129] but the practical application of these dynamic tests in the clinical setting is a challenge. A more convenient approach is to measure a random, fasting, or postprandial C-peptide.[117] It is important to measure C-peptide with a concomitant serum glucose (eg, glucose >72 mg/dL [>4 mmol/L]) as hypoglycemia will suppress C-peptide. Individuals with DKA or severe hyperglycemia should wait at least 2 weeks from resolution of glucotoxicity (β-cell toxicity) before checking C-peptide.[130,131] As per a joint consensus report from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), a low C-peptide value (<200 pmol/L [0.6 ng/mL] within 5 hours of a meal) combined with ≥1 positive T1D Ab in a person <35 years of age is suggestive of T1D.[130,131] Conversely, for adults >35 years of age who are taking insulin, a C-peptide ≥600 pmol/L (1.8 ng/mL) is most consistent with T2D.[130,131] C-peptide levels of 200 pmol/L (0.6 ng/mL) to 600 pmol/L (1.8 ng/mL) are indeterminate but could be consistent with T1D or maturity-onset diabetes of the young (MODY),[130,131] so clinicians should be cautious when interpreting an indeterminate C-peptide as being indicative of T1D when there is an absence of β-cell autoantibodies.

If a diagnosis of T1D is established, insulin treatment is needed. Individuals with LADA may not require insulin at the onset of disease if C-peptide is still ≥300 pmol/L (1.8 ng/mL),[117] and there is the possibility of using other glucose-lowering agents (metformin, GLP-1 RA, DPP-4i, TZD, or SGLT2i), but there is a lack of strong clinical evidence for benefit in this population. Caution is needed for the use of SGLT2i due to risk of euglycemic DKA if β-cell function wanes.[117] SUs/GLNs are not recommended in LADA due to concerns regarding the impact on the deterioration of β-cell function.[117]

Step 5. Assess for Other Types of Diabetes (not T1D or T2D)

Individuals may have history or physical examination findings that suggest an alternate form of DM other than T1D and T2D. Such individuals should be referred to endocrinology for further evaluation.

DM can develop secondary to Cushing syndrome and acromegaly. The diagnosis and management of both endocrine conditions are complex, and suspicion should prompt referral to an endocrinologist for appropriate testing and interpretation. The approaches to management of DM induced by Cushing syndrome and acromegaly include treatment of the primary disease (surgical removal of the culprit neoplasm and/or treatment with medical therapy), as this can result in DM remission in some cases,[132-134] and there are subtleties to the pharmacologic management of hyperglycemia secondary to Cushing syndrome or acromegaly that have been reviewed elsewhere.[135-137] Aside from overt Cushing syndrome, in individuals with milder forms of hypercortisolism, such as with autonomous cortisol secretion from an adrenal

VACCINE RECOMMENDATIONS FOR ADULTS WITH DIABETES MELLITUS

CDC IMMUNIZATION RECOMMENDATIONS FOR ADULTS WITH DIABETES MELLITUS[a]

VACCINE	RECOMMENDATION
Age-Appropriate Vaccines	All people should receive according to the CDC/ACIP immunization schedules.
COVID-19	One or more doses per current CDC recommendations and FDA approvals
Hepatitis B	Adults ≤59 years: Complete a 2-, 3-, or 4-dose series Adults ≥60 years: Based on risk and quality of immune response
Influenza	Annually
Pneumococcal	Adults with DM ages ≥19 years: • 1 dose PCV21 OR • 1 dose PCV20 OR • 1 dose PCV15 followed by PPSV23 at ≥1 year (or ≥8 weeks for adults who are immunocompromised) Also see current CDC recommendations for details.
RSV	Adults with DM ≥60 years: One dose Adults ≥50 years: One dose for those at increased risk for severe RSV[c]
TDAP	Every 10 years following completion of the primary series
Zoster (RZV)	All adults ≥50 years: Two doses 2 to 6 months apart

CDC STANDARDS FOR ADULT IMMUNIZATION PRACTICE[b]

ASSESS	**Assess immunization status of all individuals at every encounter.** • Incorporate into workflow. • Stay up to date on the latest recommendations of the CDC Advisory Committee on Immunization Practices. Updated immunization schedules are released annually.
RECOMMEND	**STRONGLY recommend vaccines based on age/risk factors.** • Address questions and concerns. • Highlight positive experiences and benefits of vaccines.
ADMINISTER/ REFER	**Administer or refer patients for immunization.** • Stock routine vaccines or know your local vaccine providers for referral.
DOCUMENT	**Document receipt of vaccine in-state immunization registry and electronic health record.**

[a]https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-age.html. For child/adolescent specific recommendations, see https://www.cdc.gov/vaccines/hcp/imz-schedules/child-adolescent.html
[b]https://www.cdc.gov/vaccines-adults/hcp/imz-standards/index.html
[c]High risk for severe RSV: DM complicated by CKD, neuropathy, retinopathy, end-organ damage, on insulin, on SGLT2i. Also, chronic cardiovascular, pulmonary, liver disease and/or severe obesity (BMI >40 kg/m^2). https://www.cdc.gov/rsv/hcp/clinical-overview/index.html

Abbreviations: **ACIP**, Advisory Committee on Immunization Practices; **CDC**, Centers for Disease Control and Prevention; **COVID-19**, coronavirus disease 2019; **DM**, diabetes mellitus; **FDA**, U.S. Food and Drug Administration; **PCV**, pneumococcal conjugate vaccine; **PPSV23**, pneumococcal polysaccharide vaccine; **RSV**, respiratory syncytial virus; **RZV**, recombinant zoster vaccine; **SGLT2i**, sodium glucose cotransporter 2 inhibitor; **TDAP**, tetanus, diphtheria, acellular pertussis

Algorithm Fig. 11. Vaccine recommendations for adults with type 2 diabetes mellitus.

nodule, the classical Cushingoid signs may not be present, while metabolic issues predominate. Results from the CATALYST trial demonstrated that, in adults meeting the study definition of difficult-to-control T2D, there is a high prevalence of hypercortisolism (23.8%), as determined by a nonsuppressed morning cortisol (>1.8 mg/dL [50 nmol/L]) after 1 mg dexamethasone overnight, and this prevalence was even higher in participants on multiple BP-lowering medications (36.6%).[138] Adrenal imaging abnormalities were found in 34.7% of those with an abnormal suppression test, of which 65.8% were unilateral adrenal nodules.[138] This finding is intriguing and a follow-up report showed that treatment (24 weeks) with the glucocorticoid receptor antagonist, mifepristone, improved weight, waist circumference, and A1C (-1.5% or -16 mmol/mol),[139] intimating that cortisol may be a culprit rather than a bystander.

A distinct type of DM may occur in the setting of pancreatic disease, sometimes referred to as type 3C, pancreatic, or pancreatogenic DM. A variety of disease states can cause this form of DM including pancreatic cancer, pancreatectomy, chronic pancreatitis, cystic fibrosis, and hemochromatosis.[140-142] The clinical presentation typically includes weight loss in the absence of insulin therapy caused by hyperglycemia from low endogenous production of insulin, as evidenced by a low C-peptide. Individuals with pancreatic DM are generally insulin sensitive as they also lack glucagon secretion, making them prone to hypoglycemia. Testing for T1D Ab will be negative. Insulin therapy is required for the treatment of pancreatic DM.

MODY, a type of monogenic DM, includes several variant subtypes with discrete gene variants and genetic testing is used to uncover the diagnosis.[130,131,143] MODY is often misdiagnosed as T2D or T1D. A family history of DM in 3 consecutive generations or a personal history of DM diagnosed <6 months of age should both raise suspicion for this entity. Laboratory studies will demonstrate negative T1D Ab, with normal or low C-peptide. Optimal management depends on the specific gene variant identified.[144,145] The Exeter Diabetes App includes a MODY calculator that can be helpful for determining the probability of MODY based on an individual's clinical characteristics (www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator).[146,147]

Medication-induced DM includes several distinct types of DM. Glucocorticoid-induced DM is well known to exacerbate existing DM or induce new-onset hyperglycemia.[148] Posttransplant DM develops after organ transplant and in the setting of use of immunosuppressive agents, including glucocorticoids, which increase insulin resistance, and the calcineurin inhibitor tacrolimus, which has direct and negative effects on β-cell function and also promotes insulin resistance and enhances intestinal glucose uptake, further exacerbating hyperglycemia.[149-152]

Checkpoint inhibitor-associated autoimmune DM (CIADM) has an incidence of <1% to 2%. The onset of CIADM can be fulminant and severe, and often presents with DKA, due to rapid β-cell destruction. T1D Abs are positive in approximately 50% of individuals, combined with low C-peptide.[153,154] CIADM requires insulin therapy and is irreversible.

Other forms of DM are rare but may be considered in the context of the clinical presentation. Mitochondrial DM is maternally inherited and is classically associated with both DM and deafness.[155] Lipodystrophy can be clinically manifest by loss of subcutaneous fat and features of insulin resistance on physical exam combined high triglycerides (TGs) and MASLD.[156] These rare forms of DM should be under the care of an endocrinologist because there are important nuances to the management of hyperglycemia.

Algorithm 4. ASCVD Risk Reduction Algorithm: Dyslipidemia

Treatment of dyslipidemia (Algorithm Fig. 4) is an essential component of comprehensive prediabetes and DM management to decrease ASCVD risk. The combined effects of insulin deficiency, insulin resistance, and hyperglycemia cause multiple disruptions in lipoprotein metabolism.[157-162] This leads to an especially atherogenic state characterized by increased levels of apolipoprotein B—containing particles, including TG-rich very—low-density lipoprotein, intermediate-density lipoprotein, and remnant particles resulting in low levels of high-density lipoprotein-cholesterol (HDL-C) and increased levels of small, dense, low-density lipoprotein cholesterol (LDL-C).[163-165] Additional detailed guidance for management of dyslipidemia is available in the 2025 AACE Guideline on Pharmacologic Management of Adults with Dyslipidemia[13] and the accompanying 2025 AACE Algorithm for Management of Adults with Dyslipidemia.[12]

Step 1. Assess Lipid Panel at First Visit or at Diagnosis

All adults with prediabetes or T2D should be screened with a lipid panel at diagnosis. The standard lipid panel includes total cholesterol, TG levels, HDL-C, and LDL-C. Fasting lipid panels are not necessary for therapeutic decisions on ASCVD risk, and non-fasting lipid panels may aid timely blood draws.[166] However, a fasting sample may still be needed for assessment and management of hypertriglyceridemia.[12]

Evaluation should begin with a medical, family, and nutrition history and a review of all medications, over-the-counter medications, and supplements. Secondary causes of dyslipidemia should be excluded. An individual may have a contributing, underlying medical condition or medication, and intervention may improve or resolve the lipid abnormalities. Laboratory testing for thyroid, renal, and liver function may expose secondary causes. Adults with baseline LDL-C >190 mg/dL should be investigated for familial hypercholesterolemia. With extremely high TG levels, a diagnosis of familial chylomicronemia syndrome is a possibility. For both aforementioned lipid disorders, referral to a lipid specialist for assessment and management is recommended. Additional secondary causes of dyslipidemia include medical conditions such as overweight or obesity, hyperglycemia, hypothyroidism, pregnancy, stage 3 CKD (particularly with albuminuria), nephrotic syndrome, cholestatic disease, lipodystrophy, paraproteinemia (eg, dysgammaglobulinemia, multiple myeloma), and chronic inflammatory conditions (eg, rheumatoid arthritis, systemic lupus erythematosus).

Medications that can cause or exacerbate dyslipidemia include oral estrogens and progestins, anabolic steroids, selective estrogen receptor modulators, highly active antiretroviral therapy such as protease inhibitors, immunosuppressive medications (eg, cyclosporine, mammalian target of rapamycin kinase inhibitor), glucocorticoids, retinoids, interferon, taxol derivatives, L-asparaginase, cyclophosphamide, atypical antipsychotic agents, β-blockers, and thiazide diuretics. Although bile acid sequestrants can reduce cholesterol, these agents may also increase TG levels and should be used cautiously in individuals with elevated TG levels. In addition, TG levels and LDL-C levels may change as glycemic control improves, so the impact of initiation of glucose-lowering therapy must be considered when adding or titrating lipid-lowering therapies.

Step 2. Initiate Lifestyle Intervention

A common secondary cause of dyslipidemia is a diet that is high in carbohydrates and/or simple sugars combined with a sedentary lifestyle. Excessive alcohol consumption also contributes to dyslipidemia, particularly hypertriglyceridemia; minimization of alcohol consumption should be encouraged. Adults with dyslipidemia should be provided with tools to promote weight loss and achieve a healthy weight. A 5% loss of body weight improves TG levels and there is continued decline in TG levels even at >15% weight loss.[167] Counseling on lifestyle interventions is essential and should include advice on a healthful diet (whole-foods, plant-based, Mediterranean, and DASH diets); avoidance of processed foods, saturated fat, simple carbohydrates, white starches, and added sugars; and increased intake of dietary fiber (30—40 g per day) and lean proteins (eg, fish, lean meat, and skinless poultry).[168] Regular physical activity should be encouraged and ideally should include a minimum of 150 minutes per week of moderate-intensity activity divided into 3 to 5 sessions per week, along with 2 resistance training sessions per week.[168]

Step 3. Assess Risk

Assessment of an individual's ASCVD risk category helps determine the lipid treatment targets and direct appropriate lipid-lowering therapy. For primary prevention, established 10-year risk categories for ASCVD are low (<7.5%), intermediate (7.5%—20%) and high (>20%).[12] T2D over 40 years of age (or younger if at increased ASCVD risk) confers automatic intermediate to moderate risk. Individuals with familial hypercholesterolemia, HIV, metabolic syndrome, MASLD, CKD, and chronic inflammatory diseases are also considered to be at intermediate to high risk.[12,13] When the decision to initiate pharmacotherapy is uncertain, a validated risk calculator can estimate 10-year risk for ASCVD (Table 1). For individuals with intermediate calculated risk, the presence of additional risk enhancers (eg, family history, elevated TG/non—HDL cholesterol, and CKD) may result in reclassification to high risk. The routine use of ancillary risk markers (apolipoprotein B, lipoprotein[a], high sensitivity C-reactive protein, coronary artery calcium score) are not recommended by the 2025 AACE Guideline on Pharmacologic Management of Adults with Dyslipidemia[13] because the task force determined that, based on currently available evidence, there was limited added benefit when already using a validated risk assessment tool. However, there may be some utility for reclassification of intermediate to high risk if it impacts therapy. Risk calculators are appropriate for determining risk for primary prevention, but adults with established ASCVD are already considered high risk and should be treated for secondary prevention.

Step 4. Initiate a Statin as First-Line Therapy

Treatment of individuals at low risk should focus on lifestyle modifications. For adults at intermediate risk, a moderate-intensity statin (30%—40% LDL-C—lowering) is appropriate while for those at high risk, a high-intensity statin (50%—60% LDL-C—lowering) is indicated (Table 2).[10,169] The majority of adults with T2D have an indication for a high-intensity statin. Although statins have been shown to increase glucose levels, the effect is minimal

Table 1
Atherosclerotic Cardiovascular Disease Risk Calculators

Calculator	URL
American Heart Association PREVENT Calculator[a,b]	https://professional.heart.org/en/guidelines-and-statements/prevent-risk-calculator/prevent-calculator
American College of Cardiology Pooled Cohort Equations ASCVD Risk Estimator Plus	https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/
Framingham Heart Study CVD Risk Calculator	https://www.framinghamheartstudy.org/fhs-risk-functions/hard-coronary-heart-disease-10-year-risk/
European Society of Cardiology SCORE2, SCORE2-OP[c] and SCORE2-Diabetes[a]	https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts https://www.mdcalc.com/calc/10510/score2-diabetes
PAHO Cardiovascular Risk Calculator[d]	https://www.paho.org/en/hearts-americas/cardiovascular-risk-calculator-app
MESA Risk Score[a,e]	https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx
QRISK[a]	https://qrisk.org/

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; MESA = Multi-Ethnic Study of Atherosclerosis; PAHO = Pan American Health Organization.
[a] Includes hemoglobin A1c or diabetes mellitus status.
[b] Separate calculators for CVD and ASCVD (coronary disease and stroke); includes ZIP code for estimate of health disparities.
[c] European populations and SCORE2-OP for individuals >79 years of age.
[d] 45–75 years of age range in Latin American and Caribbean populations.
[e] 45–85 years of age range in Caucasian, Chinese American, African American, or Hispanic populations.

Table 2
Statin Therapy

Statin	Low Intensity	Moderate Intensity	High Intensity
Simvastatin	10 mg	20–40 mg	—
Pravastatin	10–20 mg	40–80 mg	—
Lovastatin	20 mg	40 mg	—
Fluvastatin	20–40 mg	40 mg BID/80 mg XL	—
Pitavastatin	1 mg	2–4 mg	—
Atorvastatin	—	10–20 mg	40–80 mg
Rosuvastatin	—	5–10 mg	20–40 mg

Abbreviation: BID = twice daily.
Modified from Blonde et al[10] and Stone et al.[169]

and outweighed by CV benefits.[170] For individuals with prediabetes, the benefits of statin therapy should be weighed in the context of the ASCVD risk score and the minor risk of progression to T2D with statin use,[171] which tends to occur in those who are closer to the threshold for diagnosis of T2D.[172,173] Of the available risk calculators, the American Heart Association PREVENT Calculator and the European Society of Cardiology SCORE2-Diabetes provide for entry of A1C values.

Residual risk can persist even with maximally tolerated statin therapy in individuals with multiple risk factors and those with stable clinical ASCVD. Lipids should initially be monitored at 6- to 12-week intervals to determine if intensification of therapy is needed and then at less frequent intervals (eg, 6 months) once lipid goals are attained.

Some people may manifest statin intolerance. The FDA–accepted definition of statin-induced myopathy is pain or weakness accompanied by a creatine kinase (CK) level >10-fold the upper limit of the normal laboratory range, but this is rare (<0.1% over placebo in clinical trials). The risk of severe rhabdomyolysis with CK >40-fold the upper limit of normal is approximately 1 to 4 in 10,000 per year.[174] However, statin-associated muscle symptoms (SAMS) are more commonly characterized by myalgias, weakness, tenderness, and the causality is not always clear.[174,175] The overall incidence of statin intolerance is in the range of 5% to 20%, with lower rates in placebo-controlled trials; clinical trials with direct queries about muscle symptoms did not show a significant difference in the rates of muscle symptoms among participants in statin and placebo groups.[174] SAMS may resolve with discontinuation and recur when rechallenged with the same or alternative statin. Management includes acknowledging the symptoms and considering testing the CK. The 2025 AACE Algorithm for Management of Adults with Dyslipidemia provides comprehensive guidance for investigating and managing SAMS, including integration of CK levels in decision making.[12]

Risk factors for myopathy include age >65 years, female sex, low BMI, East Asian heritage, history of muscle symptoms, impaired renal and/or hepatic function, DM, HIV infection, concomitant medications (eg, fibrates, erythromycin, fluconazole), vitamin D deficiency, hypothyroidism, and acute infection.[12,168] Drug interactions should be considered, particularly for concomitant medications and statins that have high first-pass metabolism and are metabolized through CYP3A4 (eg, simvastatin, lovastatin, atorvastatin). When symptoms resolve, and if myopathy was mild, a rechallenge with a lower dose or less frequent dosing (eg, alternate days), or use of a hydrophilic statin with less association with myopathy (eg, pravastatin, rosuvastatin) may increase tolerance of statin therapy. Even though observational studies have shown that normalization of 25-hydroxy-vitamin D_3 levels[176] may help with SAMS, a secondary analysis of the VITamin D and OmegA-3 Trial (VITAL) revealed that the frequency of statin-induced myopathy did not differ with vitamin D supplementation compared with placebo.[177]

Step 5. Intensify Therapy to Achieve Lipid Targets

In adults with T2D, additional laboratory testing of lipid levels should be undertaken at frequent intervals (every 3–6 months) to direct titration of the statin or addition of an adjunct therapy to achieve lipid targets. Less frequent testing intervals can be considered once lipid goals are consistently achieved. For individuals with ASCVD or at increased risk of ASCVD, including those with T2D, AACE issued a conditional recommendation for an LDL-C target of <70 mg/dL (1.8 mmol/L) based on meta-analyses of numerous trials, showing only a moderate decrease in risk of myocardial infarction (MI) and trivial to no impact on other CV events and mortality with a lower LDL-C target.[12,13] For very high-risk individuals with clinical ASCVD (acute coronary syndrome, previous MI, stroke, peripheral artery disease), a lower LDL-C threshold of <55 mg/dL (<1.4 mmol/L) has been recommended by other organizations[178] and a previous guideline from AACE.[179] This cutoff was derived from the results of IMPROVE-IT (The Improved Reduction of Outcomes: Vytorin Efficacy International Trial),

where the combination of simvastatin with ezetimibe achieved an LDL-C level of 53 mg/dL (1.4 mmol/L) and resulted in a modest relative risk reduction of 6% for major adverse cardiovascular events (MACEs) in participants who had a recent hospitalization for acute coronary syndrome.[180,181] Subsequent meta-analyses did not observe differences in relative risks for CV events and mortality in individuals achieving lower LDL-C targets. Overall, there can be considerable medication costs associated with a lower LDL-C target that has to be balanced with the strength of the evidence and the degree of benefit for reduction in MACE.[181]

If lipid targets cannot be achieved with maximally tolerated statin therapy, then additional therapies should be considered, usually with the addition of ezetimibe (10 mg/day) to inhibit cholesterol absorption. If treatment goals are not met on a maximally tolerated statin combined with ezetimibe, additional therapy with bempedoic acid (an adenosine triphosphate citrate lyase inhibitor), a proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal Ab (mAb), alirocumab or evolocumab, or a bile acid sequestrant (colesevelam, colestipol, cholestyramine) are options. Bempedoic acid can cause hyperuricemia (in ≤3% of users) and should be used with caution in those with a history of gout. Tendon rupture also has been reported with bempedoic acid, with increased risk for those with a previous history of tendon problems, those taking corticosteroids or fluoroquinolones, or those with renal failure. Bile acid resins may decrease absorption of other oral medications (eg, levothyroxine), so this should be considered before initiation. Inclisiran is a small PCSK9 interfering RNA that decreases LDL-C levels. While we await data to support improved CV outcomes with inclisiran, AACE suggests use of the mAb-based PCSK9 inhibitors that provide a small CV benefit in individuals with ASCVD or at increased risk of ASCVD and on maximally tolerated statins.[12] When considering use of a PCSK9 inhibitor, it is important to consider cost, access, and the risk of ASCVD events in those with an LDL-C above goal in spite of maximally tolerated statin therapy. Evolocumab has received approval from the FDA for use in adults at increased risk for MACEs[182] (specifically CV death, MI, stroke, unstable angina requiring hospitalization, or coronary revascularization), while alirocumab is approved for use in those with already established ASCVD.[183]

For individuals with true statin intolerance, a change in therapy may be the only recourse and switching to bempedoic acid, a PCSK9 mAb, or a bile acid resin can be considered depending on person-specific characteristics.

Step 6. Hypertriglyceridemia Management

Management of hypertriglyceridemia requires intensification of lifestyle with tight adherence to a healthy diet (eg, avoidance of simple carbohydrates, fruit juices, and alcohol). Clinicians also should look for secondary causes contributing to hypertriglyceridemia such as concomitant medications (estrogens, retinoids, anti-rejection drugs, L-asparagine) and hypothyroidism, among other disorders.[12] For individuals with T2D, tightening glycemic control also may be needed.

In patients with hypertriglyceridemia, prevention of ASCVD remains a treatment priority and statins are first-line therapy, while fibrates are reserved for prevention of pancreatitis in the setting of severe hypertriglyceridemia. Pancreatitis risk is increased for TG levels >500 mg/dL (5.6 mmol/L) and particularly if TG levels are >885 mg/dL (10.0 mmol/L).[12] For individuals with T2D and TG levels >200 to 500 mg/dL (>2.3–5.6 mmol/L), on a background of an optimally dosed statin and an LDL-C at goal, the addition of a fibrate has not been proven to decrease MACEs. In the PROMINENT trial (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes), the incidence of MACE with TG levels >200 mg/dL (>2.3 mmol/L) was not reduced by pemafibrate despite lowering of TG, very–low-density lipoprotein cholesterol, remnant cholesterol, and apolipoprotein C-III levels by 26% to 28%.[184] This aligned with the findings of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, which did not find benefit for the addition of fenofibrate to simvastatin for MACEs.[185] Subgroup analyses of the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study and meta-analyses reported that adults with T2D and elevated TG levels (>200 mg/dL [>2.3 mmol/L]) and/or low HDL-C (<40 mg/dL [<1.03 mmol/L]) may derive some ASCVD benefit from the addition of a fibrate.[10,186-189] However, a meta-analysis of 12 trials (53,271 participants) found that, although treatment with fibrates was associated with decreased MACE, the effect was attributable and proportionate to lowering of LDL-C.[190] AACE does not recommend the addition of fibrates to a statin to decrease ASCVD risk for individuals with T2D,[12,13] and the first priority should be to reduce LDL-C to goal with a maximized statin and additional LDL-C lowering therapy when indicated.

The REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) demonstrated that the addition of icosapent ethyl (IPE) to statin therapy positively reduced CVD events by 25% in participants with T2D and TG levels >135 mg/dL (>1.5 mmol/L) and ASCVD or age >50 years and a second CV risk factor, although this effect was independent of TG and LDL-C lowering.[191] Potential concerns about the magnitude of the beneficial effect of IPE with use of the mineral oil placebo in REDUCE-IT have been voiced, but overall, IPE can be added if TG levels are 150 to 499 mg/dL (1.7–5.6 mmol/L) in adults with T2D at LDL-C goal on a maximally tolerated statin and with established ASCVD or ≥2 additional traditional CVD risk factors. The use of other omega 3 fatty acid formulations containing both eicosopentaenoic acid (EPA) with docosahexaenoic acid (DHA) are not recommended because of a lack of benefit for adults at high risk for ASCVD,[13] as demonstrated by the STRENGTH trial.[192]

Fibrate therapy can be added to reduce the risk of pancreatitis in adults with hypertriglyceridemia ≥500 mg/dL (5.6 mmol/L).[13] Prescription grade omega-3 fatty acids (EPA or EPA/DHA) can be considered with a caution that there can be increased risk for atrial fibrillation, bleeding, and an increase in LDL-C.[13] Niacin is not recommended by AACE for use in hypertriglyceridemia, including severe hypertriglyceridemia.[13] For individuals with persistent TG >885 mg/dL (10 mmol/L), referral for genetic testing for familial chylomicronemia syndrome should be considered as it may impact the choice of therapy to prevent acute pancreatitis. Olezarsen is an apolipoprotein C-III inhibitor that has regulatory approval as an adjunct to low-fat diet for familial chylomicronemia syndrome.[193] In the Balance trial, there was a 90% reduction in episodes of acute pancreatitis in the olezarsen treated group.[193]

Algorithm 5. Atherosclerotic Cardiovascular Disease Risk Reduction Algorithm: Hypertension

HTN is prevalent among adults with T2D and increases the risk of macrovascular and microvascular complications of DM.[194] The coexistence of prediabetes and HTN also increases the risk of CV events.[195] Data from the UK Prospective Diabetes Study demonstrated that increased BP control in adults with T2D decreased the risk of death related to DM and micro- and macrovascular complications, and the favorable risk-benefit profile of intensive BP control on ASCVD risk has been confirmed in subsequent clinical trials that included participants with T2D.[196-200]

Although there are clear pathophysiologic mechanisms that link T2D to HTN, secondary causes of HTN should be considered

and ruled out. Primary hyperaldosteronism is an underdiagnosed and treatable cause of secondary HTN and is highly prevalent in individuals with T2D, estimated at approximately 10% to 20% of adults in some studies.[201-203] The most recent guidance for primary hyperaldosteronism provides a conditional recommendation to screen all adults with HTN using a plasma aldosterone concentration and plasma renin activity (or direct renin concentration).[201] However, interpretation of testing can be complex, particularly in the context of potentially interfering antihypertensive medications. Individuals with a positive screening test can require referral to an endocrinologist or a HTN specialty clinic for further assessment and confirmation. Spironolactone or eplerenone are the rational choices to treat primary hyperaldosteronism if surgical intervention (eg, unilateral adrenal disease) is not possible.

AACE historically has set a systolic BP goal for the majority of adults with T2D as <130 mm Hg with a diastolic BP goal of <80 mm Hg (Algorithm Fig. 5).[10] A lower target can be considered for adults with micro- or macroalbuminuria, those at moderate/high risk for ASCVD or with established ASCVD, peripheral vascular disease, or retinopathy. It is recognized that some adults with T2D may not tolerate a goal of <130/80 mm Hg, including those with orthostatic hypotension from autonomic, acute coronary syndrome (acute MI or unstable angina), frailty, or medication intolerance.

The accuracy of BP measurement in the clinic should be ensured using appropriately maintained and calibrated equipment, trained and proficient medical staff, and correctly sized cuffs for individuals in appropriate positions (ie, sitting in a chair with feet on floor, arm supported at heart level). Ideally, serial measurements should be taken and averaged. Twenty four−hour ambulatory BP monitoring has been shown to correlate better with ASCVD risk than clinic BP measurements and it can help to identify individuals with "masked HTN" (normal BP in clinic but elevated outside of the clinic) and a lack of the normal nocturnal decrease in BP, which are both common findings in adults with T2D and can contribute to increased ASCVD risk, end organ damage, and mortality.[204,205] Home BP monitoring by individuals with T2D also may improve adherence to pharmacotherapy and success in reaching BP goals.[206,207] The recommended interventions for the management of HTN in adults with prediabetes and DM are outlined below.

Step 1. Initiate Lifestyle Interventions

Weight loss of 5% can lower BP, with the largest impact in adults who lose 10% to >15%.[167,208] Physical activity several times per week is also an important component in the treatment of HTN, because there are reductions in both systolic and diastolic BP with endurance (aerobic) and dynamic resistance training (involving motion and sources of resistance such as free weights, resistance bands, exercise machines or leveraging body weight).[209] Individuals also should be counseled about limiting dietary sodium, such as is prescribed with the DASH diet, which has been shown to improve 10-year ASCVD risk by 10%.[210,211] Mediterranean diets also have been demonstrated to lower BP and the PREDIMED study, which included participants with T2D, reported improved primary prevention of ASCVD risk with an approximate 30% decrease in the primary composite end point of acute MI, stroke, or death from CV causes over 5 years.[212,213]

Step 2. Start an Angiotensin-Converting Enzyme Inhibitor or Angiotensin II Receptor Blocker

Angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) are considered first-line therapies for HTN in adults with T2D, particularly in those with elevated urine albumin-to-creatinine ratio (UACR) >30 mg/g. Both classes appear to be equally efficacious, but there is no additional benefit for coadministration of an ACEi and an ARB together, and combination may cause harm.[214-217] The direct renin inhibitor aliskiren also should not be combined with an ACEi or ARB. The ALTITUDE (Aliskerin Trial in Type 2 Diabetes Using Cardiorenal Endpoints) clinical trial data revealed significant safety concerns in study participants with T2D and CKD and/or CVD on an ACEi/ARB who received aliskerin primarily due to adverse events of hyperkalemia and hypotension, without significant improvement in renal or ASCVD outcomes.[218] The ARB or ACEi dose should be titrated up on a regular basis (minimum every 2−3 months) to reach the BP goal. For those who manifest intolerance to an ACEi (eg, cough), an ARB can be substituted. Thiazide diuretics and dihydropyridine calcium channel blockers (CCBs) also are effective as initial therapy for BP lowering so they may be another acceptable first line choice in the absence of evidence of DM-related kidney disease and microalbuminuria, where the evidence is more robust for ACEi/ARBs. If a person's initial BP is >150/100 mm Hg, dual therapy may need to be used at the outset to reach BP goals (see Step 3. Add-on Therapy).

Step 3. Add-on Therapy

If the BP goal is not achieved with optimally titrated ACEi or ARB therapy alone, additional add-on therapy is needed. Other antihypertensive agents also have shown efficacy in slowing estimated glomerular filtration rate (eGFR) decline in individuals with T2D and HTN, including diuretics and CCB.[219] A thiazide diuretic (eg, hydrochlorothiazide, chlorthalidone, indapamide) is an effective second-line antihypertensive, and there are numerous combination pills with ACEis or ARBs with the potential to increase adherence. Dihydropyridine CCBs (eg, amlodipine or nifedipine) also can be considered as add-on therapies.

Many adults with HTN require multiple antihypertensive medications to achieve their goal BP.

The steroidal mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone should be considered for add-on therapy in individuals with resistant HTN (>140/90 mm Hg on 3 medications, including a maximum-dose diuretic). The PATHWAY-2 study showed that the addition of low dose spironolactone (25−50 mg) to a combination of an ACEi/ARB, a CCB, and a diuretic (eg, thiazide) was most effective for further BP lowering compared with placebo, peripheral α1 blocker (doxazocin), or β1 blocker (bisoprolol), across an array of renin levels.[220] These findings confirmed that sodium retention is a key underlying cause that needs to be addressed in adults with resistant HTN.[220] When adding an MRA to an ACEi or ARB, potassium levels and kidney function should be monitored approximately 1 week after initiation and after a dose change as well as at routine visits or more frequently in those at higher risk for hyperkalemia.[221,222] There are data supporting the benefits of the nonsteroidal MRA finerenone for progression of CKD and risk of heart failure (HF), ASCVD events, and related mortality in adults with T2D and microalbuminuria (UACR ≥30-300 mg/g), macroalbuminuria (>300 mg/g), or more advanced CKD but with an eGFR ≥25 mL/min/1.73 m^2.[223-226] Although finerenone can modestly reduce systolic BP, its effects are independent of pretreatment BP levels, and regulatory approval is for risk reduction for eGFR decline, end-stage kidney disease, CV death, nonfatal MI, and hospitalization for HF in adults with CKD and T2D.[227]

Additional therapies can include α- and β-blockers. Notably, β-blockers can be associated with weight gain, thought to be secondary to decreased energy expenditure.[228,229] This may be more pronounced with older agents such as atenolol or metoprolol, so the use of newer α-β blockade (carvedilol, labetalol,

dilevalol) or β_1-selective agents (nebivolol or betaxolol) may be more weight sparing. The central α_2 agonist (clonidine) or a peripheral α_1 receptor antagonist (eg, doxazosin, prazosin, terazosin) may be needed for individuals who are still hypertensive despite multiple therapies. Hydralazine also may be an effective adjunct therapy but requires multiple doses throughout the day.

Clinicians should be aware that there may be a mild reduction in systolic BP when initiating a GLP-1 RA (~1-2 mm Hg) or SGLT2i (~3-5 mm Hg).[230-235]

Algorithm 6. Comorbidities- and Complications-Centric Glycemic Control Algorithm

Individuals with T2D experience significant morbidity caused by ASCVD, which also is the leading cause of mortality in T2D despite contemporary therapy with lipid-modifying, antiplatelet, and antihypertensive agents.[236] Therapeutic lifestyle changes remain a fundamental component of glycemic control and should include a healthy meal plan, regular physical activity, healthful behavior practices (tobacco cessation and decreased alcohol intake), and weight management. Importantly, some agents belonging to newer classes of glucose-lowering agents, particularly GLP-1 RA and SGLT2i, have been demonstrated in large, RCTs to impact MACEs, HF, and/or CKD risk in individuals with T2D. Each trial had key differences such as the proportion of participants with established ASCVD versus those at high risk for ASCVD (primary prevention), heart failure with preserved or reduced ejection fraction (HFpEF or HFrEF), or preexisting high-risk or very high-risk CKD (by Kidney Disease: Improving Global Outcomes risk stratification or KDIGO criteria). Each antihyperglycemic agent has distinct effects on all-cause mortality, MACEs, CV death, CKD, hospitalization for HF, and fatal and nonfatal stroke. Additional data also are accumulating for benefits of these medications for MASLD, which affects a majority of adults with T2D.[237,238] With an understanding of the clinical trial evidence for improved outcomes, there has been a paradigm shift from an exclusively glucose-centric approach to one that prioritizes the risk factors, complications, and comorbidities of each individual with T2D to tailor glucose-lowering pharmacotherapy (see Algorithm Fig. 6 and Algorithm Fig. 9).

HF

SGLT2is have become a cornerstone of HF treatment, earning class 1 guideline recommendations for HFrEF and significant recognition for their benefits for HFpEF, supported by robust clinical trial evidence.[239] SGLT2i therapy significantly and robustly reduces the risk of hospitalization for HF or CV death (by approximately 20%–25%) in adults with T2D, with or without ASCVD, and to improve HF-related symptoms in individuals with established HF, regardless of left ventricle (LV) ejection fraction, background glucose-lowering therapies, or HF therapies.[10,240-246] In a meta-analysis, SGLT2i use resulted in a 32% reduction in risk of hospitalization for HF and a 15% reduction in CV death compared with placebo.[247] Sotagliflozin is a dual sodium–glucose cotransporter (SGLT)-1 and SGLT2i that has regulatory approval for the treatment of HF, including for adults with T2D and ASCVD risk, but is not approved as a glucose-lowering medication.[248] An SGLT2i with proven HF benefit (dapagliflozin, empagliflozin) should be recommended as first-line treatment in adults with T2D and HF regardless of A1C goal or other glucose-lowering treatments, including metformin.

Additional clinical trial evidence is needed to understand the impact of GLP-1 RAs and GIP/GLP-1 RAs for individuals with HF. A meta-analysis that included 8 CVOTs for 8 different GLP-1 RAs showed a reduction in hospitalization for HF of 11%.[249] In early trials of participants with HFrEF, liraglutide did not decrease time to death or rehospitalization for HF, including a subgroup analysis of participants with T2D.[250] Liraglutide also did not improve LV ejection fraction compared with placebo in participants with HFrEF (with or without T2D), and there was a significant increase in heart rate (average +6 beats per minute) and serious adverse cardiac events.[251] For HFpEF, semaglutide 2.4 mg weekly injection has been demonstrated to reduce HF-related symptoms and physical limitations in individuals with T2D and obesity.[16] From the SUMMIT (Study of Tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction and Obesity) trial, in obese adults >40 years of age with HFpEF (with nearly half of participants with T2D), the GIP/GLP-1 RA tirzepatide reduced worsening HF events by 46% with a 56% reduction in HF events requiring hospitalization.[17,252] Based on available data, GLP-1 and GIP/GLP-1 RAs may have benefit in the context of obesity-related HFpEF, but there is a lack of convincing evidence for HFrEF; therefore, SGLT2is are recommended as first-line therapy for individuals with T2D and HFrEF.

Some glucose-lowering agents have been shown to cause harm and should be avoided in individuals with HF. The DPP-4i saxagliptin has been shown to increase the rate of HF hospitalizations.[253] There also was a trend for HF hospitalizations with alogliptin in a post hoc analysis of the EXAMINE trial, so caution is advised with the use of this agent for individuals with New York Heart Association (NYHA) class III or IV CHF.[254] In a meta-analysis of CVOTs, DPP-4is were neutral versus placebo for hospitalization for HF and inferior to SGLT2i and GLP-1 RA.[255] TZDs can worsen fluid retention—individuals who have symptomatic HF should not use them—and initiation of pioglitazone is contraindicated in individuals with NYHA class III or IV CHF.[256]

CKD

Nearly 50% of U.S. adults with kidney failure have DM.[257] The evidence for benefit of SGLT2is to reduce adverse renal outcomes is robust, with an approximately 38% reduction in composite outcomes, which varied across trials but included worsening of eGFR or creatinine, end-stage kidney disease with or without need for kidney replacement therapy or transplant, kidney death, or CV death.[247] Use of an SGLT2i with proven benefit (canagliflozin, empagliflozin, dapagliflozin) is recommended as foundational therapy to reduce progression of DM-related kidney disease and CVD risk for individuals with T2D. It is important to note that the eGFR thresholds for initiation or use of SGLT2i for a glycemic indication are higher than those for CKD benefit because efficacy for glucose-lowering is diminished at lower eGFR. Current FDA regulatory guidance states that empagliflozin can be used for glycemic control at an eGFR $\geq$30 mL/min/1.73 m^2, while the threshold for dapagliflozin, canagliflozin, and ertugliflozin is an eGFR $\geq$45 mL/min/1.73 m^2.[258-261] However, cumulative evidence from key clinical trials justifies lower eGFR thresholds ($\geq$20 mL/min/1.73 m^2) for cardiorenal benefit with SGLT2i of proven benefit,[10,240,244,262-266] while FDA regulatory guidance for SGLT2i use below eGFR 45 mL/min/1.73 m^2 is limited to empagliflozin[258] ($\geq$20 mL/min/1.73 m^2) and dapagliflozin[259] (to $\geq$25 mL/min/1.73 m^2.[221] There also is emerging evidence to support the combination of SGLT2i with the nonsteroidal MRA finerenone. Finerenone is recommended for individuals with CKD associated with T2D and eGFR $\geq$25 mL/min/1.73 m^2 and UACR $\geq$30 mg/g to reduce risk of eGFR decline, end-stage kidney disease, CV death, nonfatal MI, and hospitalization for HF in adults with CKD and T2D.[227] These indications are based on the improved kidney and CV composite outcomes from the FIGARO-DKD[226] and FIDELIO-DKD trials.[223]

The 180-day phase 2 CONFIDENCE trial showed that combination of finerenone with empagliflozin reduced UACR significantly more than either agent alone.[267] The benefits of combination SGLT2i and finerenone for UACR and major adverse kidney events also have been reported using retrospective analyses.[268,269]

GLP-1 RAs also are an option to reduce progression of albuminuria, eGFR decline, and ASCVD risk in individuals with T2D and CKD with eGFR 15 mL/min/1.73 m^2.[10,270,271] A pooled analysis of data from CVOTs for semaglutide and liraglutide suggested a benefit of these agents to improve kidney outcomes, particularly in those with preexisting kidney disease.[272] In the FLOW trial, semaglutide (1.0 mg weekly injection) reduced the risk of major kidney disease events (a composite of onset of kidney failure, ≥50% reduction in eGFR from baseline, and death from kidney-related or CV causes) in individuals with T2D and CKD (eGFR 50–75 mL/min/1.73 m^2 and 300–5000 mg UACR, or eGFR 25–50 mL/min/1.73 m^2 and 100–5000 mg UACR).[18] Furthermore, time to death from any cause, CVD death, and first major CVD event also were reduced.[18] These results provide evidence for use of semaglutide injection to reduce the risk of kidney and CVD outcomes in this population. The impact of oral semaglutide on a secondary endpoint of time to major kidney adverse events did not reach significance in the SOUL trial.[19]

ASCVD

Three of the available GLP-1 RA–based therapies—liraglutide, semaglutide (injection and oral), and dulaglutide—have been shown in RCTs to significantly lower the risk of composite "3-point" MACEs (nonfatal MI, nonfatal stroke, and CV death) in individuals at high risk for ASCVD.[19,273-275] A 2025 meta-analysis of GLP-1 RA CVOTs found a 14% risk reduction in MACEs in individuals with or without established ASCVD, regardless of A1C, or background glucose-lowering therapy.[276] Another meta-analysis reported a 21% reduction (hazard ratio [HR] 0.79) in risk of MACE, with consistent effects whether participants were receiving or not receiving SGLT2is at baseline.[277] This latter observation is important because it means that an individual taking an SGLT2i, such as for HF or CKD, may still derive benefit from the addition of a GLP-1 RA for ASCVD risk reduction. Only dulaglutide and oral semaglutide have FDA indication to reduce the risk of MACEs for primary prevention in adults at high risk for ASCVD, based on the results of the REWIND and SOUL trials, respectively,[19,275,278] while liraglutide and semaglutide injection are approved by the FDA for secondary prevention in individuals with established ASCVD combined with T2D or with overweight/obesity, respectively. The SURPASS-CVOT trial compared tirzepatide with dulaglutide and showed that tirzepatide was non-inferior to dulaglutide for time to first MACE events (HR 0.92, CI 0.83–1.01, $P = .086$) and superior for time to all-cause death (HR 0.84, CI 0.75–0.94, $P = .002$).[279,280]

RCTs, pooled analysis, and meta-analyses of the effects of DPP-4i on MACEs have repeatedly demonstrated that this class of incretin therapies is safe but neutral.[255,281,282]

While SGLT2is have been demonstrated convincingly to lower the risk of hospitalization for HF and improve renal outcomes, the evidence for benefit with 3-point MACEs has only been shown for select agents and with lesser impact compared with GLP-1 RAs with proven benefit. Of note, the characteristics of the high-risk primary prevention population were not consistent across all trials with SGLT2is but generally included age ≥55 years, albuminuria or proteinuria, HTN and LV hypertrophy, LV systolic or diastolic dysfunction, and/or ankle-brachial index <0.9. In individuals with T2D and ASCVD, empagliflozin and canagliflozin have both been shown to decrease 3-point MACEs compared with placebo with a HR of 0.86 for both ($P = .04$ and $P = .02$ for superiority, respectively), while results were neutral for dapagliflozin (HR 0.93, $P = .17$).[244-246] Dapagliflozin and empagliflozin significantly reduced death from CV causes (which includes death from HF) by 18% and 38% respectively, while the impact of canagliflozin was not significant.[243-246]

Therefore, when adults with T2D have established ASCVD or are at high risk for ASCVD, a GLP-1 RA with proven CV benefit (semaglutide, liraglutide, or dulaglutide) should be initiated as first-line therapy independent of A1C goal or other glucose-lowering treatments, including metformin (Algorithm Fig. 6).[10] As an alternative to GLP-1 RA, with consideration of comorbidities, potential side effects, and/or individual preferences, clinicians may initiate an SGLT2i with CVD benefit (canagliflozin, empagliflozin) to reduce MACEs with T2D and established ASCVD.[244,245] For adults with T2D and established ASCVD or at high risk for ASCVD, the use of an SGLT2i reduces the risk of hospitalization for HF regardless of background glucose-lowering therapy, CV therapy, or A1C,[10] and in adults with HF and/or CKD, SGLT2i should be initiated as first-line therapy.

Stroke/TIA

The risk of stroke is markedly increased in DM, with a study of National Health and Nutrition Examination Survey data (2013–2018) reporting an OR of 28.[283] As discussed in the section on ASCVD, the 3 GLP-1 RAs approved by the FDA to reduce the risk of MACEs, including stroke, are dulaglutide (with or without established ASCVD), liraglutide, and semaglutide SC (the latter 2 agents in individuals with established CVD).[284] Dulaglutide and semaglutide have been shown to significantly decrease nonfatal stroke by 24% and 39%, respectively, for adults with T2D at high risk for ASCVD as a stand-alone outcome outside of composite 3-point MACEs.[273-275] Across meta-analyses, GLP-1 RA appear to reduce risk of stroke by 15% to 17% in adults with T2D and prior ASCVD or at high risk for ASCVD.[10,249,285,286] In individuals with T2D and ASCVD or those at high risk for ASCVD, the use of GLP-1 RA with proven benefit is recommended to reduce stroke risk.[10] With regard to the GIP/GLP-1 RA tirzepatide, the SURPASS-CVOT showed that tirzepatide was noninferior (HR 0.91, 95% CI 0.76-1.09) to the comparator dulaglutide for nonfatal stroke, which can be considered in the context that dulaglutide reduced the risk of stroke and nonfatal stroke by 24% in the REWIND trial.[275,280]

The TZD pioglitazone appears to reduce the risk of recurrent stroke and acute coronary syndrome[287] in prediabetes and can be a consideration to reduce the risk of recurrent stroke in individuals with insulin resistance, prediabetes, or T2D and a prior TIA or stroke.[10,288-290] A meta-analysis of 3 RCTs of pioglitazone in adults with a previous stroke reported a 32% reduction in recurrent stroke and 25% reduction in future ASCVD events.[288] Using a composite of stroke or MI, a post hoc analysis of the Insulin Resistance Intervention in Stroke (IRIS) trial showed that lower doses of pioglitazone (15–30 mg) were as effective as 45 mg for prevention, but with less adverse effects.[291]

Regarding stroke and SGLT2is, 2 meta-analyses have shown that there was a reduced HR of approximately 0.5 for hemorrhagic stroke when pooling data from completed SGLT2i trials, while there was no significant impact on ischemic stroke.[292,293]

MASLD

The prevalence of steatotic liver disease is extremely high in adults with T2D and estimated at 65% globally[294]; a finding of hepatic steatosis in individuals without a significant history of alcohol use and with T2D (or metabolic syndrome) is sufficient for diagnosis of MASLD, which is the updated term for nonalcoholic

fatty liver disease (NAFLD).[295] The recent change in terminology from NAFLD to MASLD reflects a growing understanding of the condition's complex relationship with metabolic health and aims to better describe its underlying mechanisms and associated risk factors. In simple terms, MASLD is a condition characterized by the accumulation of fat in the liver, often occurring alongside other metabolic cardiometabolic health issues such as obesity, T2D, high BP, and dyslipidemia. MASLD is now the most common chronic liver disease and is associated with increased risk of CV events, CKD, hepatocellular carcinoma and other extrahepatic malignancies, and liver failure[296-298] so that the identification, staging, monitoring, and management of MASLD is an imperative to improve the health of individuals with T2D. In its more severe form, MASLD can progress to MASH, which involves liver inflammation and hepatocellular injury. Both MASLD and MASH are considered serious health concerns because of their widespread prevalence and potential complications. Intensive lifestyle measures should be emphasized, particularly dietary changes, weight loss (5% for reduction in steatosis and >7% to 10% to reverse steatohepatitis and fibrosis), alcohol minimization or abstinence (with moderate to severe fibrosis), and physical activity.[299,300]

Until recently, the only pharmacotherapy with regulatory approval for the treatment of MASLD was resmetirom, a thyroid hormone receptor β agonist shown to improve fibrosis and improve or resolve MASH.[301] However, the burgeoning evidence for benefit of some subclasses of glucose-lowering agents for MASLD and recommendations for treatment have been discussed in detail in the 2022 AACE Guideline for the Diagnosis and Management of Non-Alcoholic Fatty Liver Disease and a recent consensus statement from the American Diabetes Association.[299,300] The current state of evidence for glucose-lowering agents in MASLD has been reviewed,[302] and the impact on hepatic steatosis, steatohepatitis, and fibrosis are summarized in Algorithm Fig. 9, Profiles of Pharmacotherapy for T2D.

GLP-1 RA should be considered as a first-line therapy for MASLD. Semaglutide weekly injection (2.4 mg) recently received approval by the FDA for use in MASLD based on outcomes at 72 weeks from the ESSENCE trial which showed resolution of MASH in 63% of participants (vs 34% of placebo) with reduction in fibrosis in 37% (vs 22% of placebo) and resolution without worsening of fibrosis; one-third of participants had both outcomes.[20] Before the ESSENCE trial, previous clinical trials using GLP-1 RA had small sample sizes (exenatide,[303] liraglutide,[304] dulaglutide,[305] and semaglutide[306]) but encouraging findings and network meta-analyses of 14 clinical trials in MASLD/MASH support the positive impact of GLP-1 RA as therapy for MASLD.[307,308] Current research is focused on GLP-1 RAs with additional agonism (eg, GIP, glucagon), which may provide advantages over GLP-1 RAs alone.[309-313] The dual GIP/GLP-1 RA tirzepatide was recently shown to resolve MASH in 40% to 60% of participants (10% of placebo) in a dose-dependent manner (tirzepatide 5–15 mg), and half of participants had a decrease in fibrosis by at least one stage.[21] Although the trial population was not limited to individuals with T2D, the majority (55%–60%) of participants had T2D. Tirzepatide does not have regulatory approval for MASLD indication at this time, but it may be an appropriate choice for individuals who meet other prescribing criteria.

Several RCTs have demonstrated that pioglitazone can improve key liver histologic features, such as steatosis, inflammation, and hepatocellular ballooning, although its effects on fibrosis have been less consistent.[314-321] These findings have led to recommendations for a more prominent position for pioglitazone for the treatment of individuals with T2D who also have liver steatosis or MASH with moderate to severe fibrosis.[299,300] Pioglitazone causes dose-dependent weight gain of approximately 1% to 2% with 15 mg per day ranging to 3% to 5% with 45 mg per day, partially because of fluid retention, but also increased subcutaneous adipose tissue. Pioglitazone-induced weight gain can be mitigated by concomitant GLP-1 RA or SGLT2i therapy.[302] As discussed above, pioglitazone should not be used in individuals with class III/IV NYHA CHF. In addition, pioglitazone has been associated with bone loss and the development of osteoporosis and fractures, particularly in postmenopausal women.

Data for SGLT2i as a therapy for MASLD are emerging. Decreases in hepatic steatosis have been observed with dapagliflozin,[322,323] empagliflozin,[324,325] and canagliflozin[326] in RCTs using noninvasive methods, primarily MRI-based techniques. A post hoc analysis of the ertugliflozin CVOT (VERTIS CV) reported decreased liver enzymes and the hepatic steatosis.[327] At this juncture, only 1 placebo-controlled RCT has used liver biopsy specimens to assess MASLD outcomes with SGLT2i therapy. Dapagliflozin significantly improved MASH and fibrosis in adults with or without T2D and biopsy-proven MASH.[328]

OSA

The SURMOUNT-OSA trial investigated the impact of tirzepatide for adults with obesity and OSA for participants with or without positive airway pressure at baseline.[15] Over the year-long trial, mean body weight decreased by nearly 20%, the apnea-hypopnea index (events/hour) decreased significantly, and scores for patient-reported outcomes for sleep-related impairment and disturbance improved significantly.[15] Approximately two-thirds of participants were characterized as having prediabetes at baseline. However, no individuals with T2D were enrolled[15]; therefore, OSA was not formally added to the Comorbidities- and Complications-Centric Glycemic Control Algorithm (Algorithm Fig. 6), although tirzepatide would be a rational option for treatment of hyperglycemia for an individual with T2D, obesity, and OSA.

Using the Comorbidities- and Complications-Centric Glycemic Control Algorithm (Algorithm Fig. 6)

As stated in the principles of management (Algorithm Fig. 1), the optimal A1C target is ≤6.5% (48 mmol/mol) for most nonpregnant adults if it can be achieved safely (without hypoglycemia) and without undue medication burden. Other glycemic targets including fasting blood glucose (FBG) and PPG also are useful to guide therapy. However, glycemic goals should be individualized. Consideration of life expectancy, disease duration, presence or absence of micro- and macrovascular complications, CV disease risk factors, comorbid conditions, and risk of hypoglycemia as well as cognitive and psychological status must be considered.[10,49] Less stringent A1C goals (eg, 7%–8%) may be adopted in adults with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced renal or CV disease, extensive comorbid conditions, or longstanding DM in whom the A1C goal has been difficult to attain despite intensive efforts as long as the person remains free of hyperglycemia-associated symptoms.[10,46,47,50] Newer antihyperglycemic agents such as GLP-1 RA and SGLT2i are associated with a lower risk of hypoglycemia unless used with SUs, GLNs, and/or insulin.

A comorbidities- and complications-centric approach in Algorithm Fig. 6 proposes that a clinician first consider the risk(s) and preexisting condition(s) for each person with T2D and use that as a basis to choose initial pharmacotherapy, independent of glucose levels, to improve the individual's outcomes. The order of complications/comorbidities (from left to right) is purposeful: HF, CKD, ASCVD or high risk for ASCVD, stroke/TIA, and MASLD. For example, if an individual has a preexisting history of HF, then an

SGLT2i with proven benefit is the first choice. The presence of additional comorbid conditions, such as known ASCVD, may also mean that another pharmacotherapy, a GLP-1 RA, should be added to address those outcomes as well. For newly diagnosed individuals with A1C >9%, or >1.5% above the glycemic target, starting 2 or more therapies is recommended to get to goal faster. Each medication should be up-titrated to the maximally tolerated approved dose and additional glucose-lowering agents should be added on to achieve glycemic targets. If comorbidities/complications have been addressed with first-line therapy, and further lowering of the A1C is needed, metformin should be considered if an individual is not already taking this agent and renal function is eGFR ≥30 mL/min/1.73 m^2. It is important to remember that most participants with T2D who were enrolled in CVOT and CKD outcomes trials also were taking metformin.

If HF, CKD, established or high-risk factors such as albuminuria, HTN for ASCVD, stroke/TIA, or MASLD are not present, then the clinician is referred to the Glucose-Centric Algorithm for Glycemic Control (Algorithm Fig. 7) and the Profiles of Pharmacotherapy for T2D table (Algorithm Fig. 9).

Algorithm 7. Glucose-Centric Glycemic Control Algorithm

The Glucose-Centric Glycemic Control Algorithm (Algorithm Fig. 7) is for determining initial and add-on therapies for adults with T2D in the absence of high risk or established HF, CKD, ASCVD, stroke/TIA, or MASLD. Although it can be argued that all individuals with T2D are at risk for some or all of these comorbidities or complications (eg, ASCVD), a definition of what constitutes "high risk" should be considered in the context of the inclusion criteria of clinical trials (eg, CVOTs) that revealed benefit for specific glucose-lowering agents.

Preferred initial pharmacotherapy is proposed depending on the clinical scenario(s) specific to an individual. For adults with symptomatic hyperglycemia (eg, catabolic symptoms such as weight loss with polyuria/polydipsia), an A1C >10%, and/or BG >300 mg/dL, which suggests marked insulin deficiency, basal insulin should be initiated to reduce glucose as safely and promptly as possible. Some adults with severe hyperglycemia may need simultaneous initiation of bolus insulin. Combination basal insulin with a GLP-1 RA or GIP/GLP-1 RA can be considered depending on the clinical picture, but with the understanding that GLP-1 RA/GIP/GLP-1 RA will require a titration phase that could delay glycemic control. SGLT2i should also be used with caution in adults with severe hyperglycemia, because individuals with A1C >10% have a higher risk of DKA with SGLT2i use.[329] When acute glucose toxicity is resolved, the possibility of using noninsulin pharmacotherapies should be revisited. Clinicians should refer to the Initiating and Titrating Insulin Algorithm (Algorithm Fig. 8) for more guidance about starting and advancing insulin therapy.

For most individuals, metformin should be initiated if there is no contraindication (eg, eGFR <45 mL/min/1.73 m^2). To maximize tolerability, metformin should be started at a low dose and titrated over the course of a few weeks to the maximally tolerated dose.[16] Given that T2D is a progressive disease, many individuals will require >1 glucose-lowering medication to achieve their individualized glycemic target. Clinicians should consider multiple factors when selecting pharmacotherapy, including presence of overweight or obesity, hypoglycemia risk, and decreased access or the need for decreased cost of medications. Individuals often present with >1 of these scenarios, so using a person-centered, shared decision-making approach is important. The order that medications are listed in the algorithm denotes the suggested hierarchy for selection. In adults with overweight or obesity and the additional goal of weight loss, tirzepatide or a GLP-1 RA are preferred options if accessible. By comparison, SLGT2i therapy may induce mild weight loss, usually in the range of 1 to 2 kg but ≤4% of body weight in some studies.[330-332] Adults with a history of hypoglycemia, at high risk of hypoglycemia, and/or at risk for severe complications from hypoglycemia should preferentially be initiated with an agent associated with low risk for hypoglycemia, including GLP-1 RA, SGLT2i, dual GIP/GLP-1 RA, TZD, or DPP-4i. For many adults with T2D, access and cost are barriers to receiving newer pharmacologic agents; in this situation, metformin with a TZD, SU, or GLN would be more economical.

In adults with newly diagnosed T2D who are drug naïve, prospective studies support the initiation of combination therapy to achieve glycemic targets more quickly as compared with a stepwise approach.[333,334] For recently diagnosed individuals with T2D and an A1C 7.5%, early combination therapy also may be considered, usually with metformin combined with another agent that does not cause hypoglycemia, particularly a GLP-1 RA, SGLT2i, or DPP-4i.[10] If a person's A1C is >9% or >1.5% above goal, >2 agents may need to be initiated at the outset.[10] Clinicians should be cognizant that combination of incretin-based therapies is not recommended (ie, DPP-4i with GLP-1 RA or dual GIP/GLP-1 RA). Medications should be titrated to the maximally tolerated dose to achieve the individualized A1C goal, and additional agents should be considered in a timely fashion to avoid therapeutic inertia. However, it is also important to consider the burdens of polypharmacy and cost for each individual when deciding on additional glucose-lowering medications. The clinician is referred to the Profiles of Pharmacotherapy for T2D (Algorithm Fig. 9) for more details regarding the glucose-lowering efficacy of each medication as well as the known risks and benefits of each medication class.

Algorithm 8. Initiating and Titrating Insulin Algorithm

The overall goal of insulin therapy is to achieve glycemic control after failure of noninsulin glucose-lowering agents. Glycemic targets should be individualized, although an A1C of ≤6.5% is recommended for most adults using insulin if it can be safely achieved with minimal or ideally no hypoglycemic events (Algorithm Fig. 8). While A1C is a key measure, insulin titration requires the use of multiple glycemic parameters including FBG, premeal or 2-hour postprandial BG, and data from CGM, when available, including TIR, TBR, GV, and GMI.[43] In general, targets for fasting and premeal glucose are <110 mg/dL (<6.1 mmol/L), but without hypoglycemia <70 mg/dL (<3.9 mmol/L) and can be individualized based on a person's comorbidities and clinical status. The use of CGM is highly recommended for individuals treated with insulin to optimize glycemic control while minimizing hypoglycemia.[42] Recommended CGM goals are that TIR (glucose range 70–180 mg/dL or 3.9–10 mmol/L) is >70%, combined with minimal TBR (<4% for <70 mg/dL [<3.9 mmol/L] and <1% for <54 mg/dL [<3 mmol/L]) and <25% time above range for >180 mg/dL (>10 mmol/L) with <5% for >250 mg/dL (>13 mmol/L).[32,40-42] GV 33% or even lower is associated with decreased risk of hypoglycemia.[32-39]

Symptomatic Hyperglycemia

As discussed above (Algorithm Fig. 7), basal insulin with or without prandial insulin treatment may be needed as initial therapy if the A1C is >10% and/or glucose values are >300 mg/dL, combined with catabolic symptoms (weight loss), polydipsia, and polyuria. A GLP-1 RA or dual GIP/GLP-1RA alone is not recommended as it requires titration and may delay glucose control. The goal of initial intensive insulin therapy for an individual with symptomatic hyperglycemia is to reduce glucose levels safely and

promptly. After improved glycemic control is achieved with initial insulin therapy, especially with a new diagnosis of DM,[335] a role for noninsulin glucose-lowering agents can be considered (see Algorithm Figs. 6 and 7).

Failure of Noninsulin Antihyperglycemic Treatments

For most adults who need intensification of glycemic control and who are already prescribed 3 to 4 oral therapies, an injectable GLP-1 RA or GIP/GLP-1 RA should be the next choice, if not already in use.

Basal Insulin Initiation

If subsequent glycemic targets are not achieved, basal insulin can be added alone or as a basal insulin/GLP-1 RA combination injection. The dose of basal insulin can be based on A1C levels at the time of initiation. For an A1C <8%, basal insulin can be started at 0.1 to 0.2 U/kg/day and for an A1C >8%, 0.2 to 0.3 U/kg/day can be considered. Analog insulins, such as glargine or degludec, are preferred over neutral protamine Hagedorn as they have reduced incidence of hypoglycemia.[10,336] After basal insulin is initiated, discontinuation of SUs is recommended. Fixed-dose GLP-1 RA and basal insulin combinations also provide improved glycemic control when basal insulin alone has not achieved targets.[337]

Depending on the half-life, daily administered basal insulin should be titrated every 2 to 3 days (glargine) or every 3 to 5 days (degludec) to reach glycemic targets. A goal FBG of <110 mg/dL (<3.9 mmol/L) without hypoglycemia is recommended in the 2022 AACE DM guideline.[10] However, glycemic goals should be individualized. Individuals taking insulin can be counseled on how to titrate insulin doses independently based on self-monitoring of BG.[338,339] One approach to titration of basal insulin is a fixed-titration regimen where basal insulin can be increased by 2 units at appropriate intervals to achieve the target fasting glucose. Another approach uses adjustable self-titration depending on the FBG, increasing by 20% if >180 mg/dL (>10 mmol/L), 10% if 140 mg/dL to 180 mg/dL (7.8–10.0 mmol/L), and 1 unit if 110 mg/dL to 139 mg/dL (6.1–7.7 mmol/L). Insulin doses should be reduced if there is fasting hypoglycemia: reduce by 10% to 20% for FBG <70 mg/dL (3.9 mmol/L) and by 20% to 40% if FBG <40 g/dL (2.2 mmol/L).

Weekly insulins have not received regulatory approval in the United States but icodec insulin has been approved in other countries. Icodec weekly was noninferior to glargine U-100 in adults with T2D receiving prior basal bolus insulin therapy with glargine[340] and also was demonstrated to have superiority for A1C lowering and TIR by CGM in insulin-naïve individuals compared with glargine.[341] Compared with daily degludec, icodec also achieved superiority for A1C lowering by 26 weeks in adults with T2D, although with a mild increase in weight (+1.4 kg).[342] A weekly injection of a combination of icodec and semaglutide (IcoSema) has been shown to improve A1C lowering while inducing weight loss (mean change -3.70 kg) compared with icodec alone (+1.9 kg).[343] IcoSema also has been compared with basal-bolus insulin therapy in an open-label trial and was non-nferior for A1C lowering (A1C -1.5% for both groups) with 3.6 kg weight loss compared with 3.2 kg weight gain in the basal-bolus group.[344] Weekly efsitora insulin also has been shown to be noninferior to degludec for efficacy in a phase 3 clinical trial but has not yet received regulatory approval.[345] Weekly insulins need titration once weekly to once every 4 weeks and hold the promise of decreasing injection burdens for those with T2D without compromising glycemic control.

It is important to realize when continued titration of basal insulin may not be ideal and an individual needs readjustment of their insulin regimen with the addition of prandial insulin. So-called overbasalization may be an issue if there are elevated PPG levels (>180 mg/dL or 10 mmol/L) but the FBG is at goal or if the basal insulin dose is >0.5 units/kg/day.[346] The BeAM score can be helpful, calculated as bedtime glucose minus morning pre-breakfast glucose and a score of >50 mg/dL may indicate that basal insulin is optimized and prandial insulin should be added to improve mealtime glucose levels.[347]

Initiation of Prandial Insulin

Rapid-acting insulin analogs are preferred over regular insulin because of their comparatively earlier onset of action in relation to a meal. Prandial insulin can be initiated at the largest meal, particularly the meal with the highest carbohydrate content, at 10% of the basal insulin dose or at 5 units. Stepwise addition to other meals is recommended as additional glycemic control is needed.[348,349] Alternatively, prandial insulin can be started at all meals simultaneously with a goal of 50% basal and 50% prandial insulin of the total daily dose divided by the number of meals.[348,349]

Although not as preferred as basal-bolus insulin regimens, fixed-dose premixed insulins that combine long- and short-acting insulins can also be considered for those who may have concerns about multiple insulins and injections. Although premixed insulin may be cost effective and requires fewer injections, it also has less flexibility for dosing adjustments and may increase the risk for hypoglycemia.[10,350] Nonetheless, premixed insulin may offer an alternative to achieve adequate glycemic control because of the simplicity of the insulin regimen and increased adherence, if administered with regularly scheduled meals. Initiation of premixed insulin can be weight based (eg, 0.2–0.3 units/kg/day), although recommendations for a starting dose units/kg vary widely, and divided into 2/3 units at the morning meal and 1/3 units at the last meal of the day. If an individual was previously on basal insulin alone, the total daily dose of basal can be used to predict total premixed insulin requirements.

Prandial Insulin Titration

Goal prandial glucose targets should be individualized.[10] Prandial insulin should be titrated every 2 to 3 days, based on the 2-hour postprandial or next preprandial glucose. One approach is to titrate prandial insulin as follows:

- For premidday meal glucose >110 mg/dL, increase the morning meal dose by 10% to 20%
- For preevening meal glucose >140 mg/dL, increase the midday meal dose by 10% to 20%
- For bedtime glucose >140 mg/dL, increase the preevening meal dose by 10%
- Premixed insulin can be titrated by 2 units every 2 to 3 days relying on the morning FBG because of the presence of basal insulin

Hypoglycemia

For premeal hypoglycemia, prandial insulin should be adjusted with the following approach:

- For premidday meal glucose <70 mg/dL (<3.9 mmol/L), decrease AM meal dose by 10% to 20%
- For preevening meal glucose <70mg/dL (<3.9 mmol/L), decrease premidday meal dose by 10% to 20%
- For bedtime glucose <70 mg/dL (<3.9 mmol/L), decrease preevening meal dose by 10% to 20%

Individuals with DM who are taking insulin and their families/companions should be educated on the symptoms and treatment of hypoglycemia and severe hypoglycemia (<54 mg/dL or 3 mmol/L) where intervention may be needed by a caretaker. If a person can safely swallow, an oral source of glucose (eg, tablets, fruit juice) should be given.[351] For a person who is unresponsive or unable to take oral glucose, glucagon should be administered. There are multiple formulations of glucagon available. While older glucagon formulations require reconstitution before subcutaneous or intramuscular injection, soluble glucagon and a glucagon analog, dasiglucagon, are available that do not require reconstitution and are ready for immediate injection.[352,353] Intranasal glucagon also has been shown to be efficacious for raising BG quickly.[354-358]

Algorithm 9. Profiles of Pharmacotherapy for Type 2 Diabetes

The table of Profiles of Pharmacotherapy for Type 2 Diabetes (Algorithm Fig. 9) provides a summary of clinically relevant information for approved medical therapies for the treatment of adults with T2D. Information is provided to remind the clinician about medication-specific efficacy (A1C lowering), benefits (ASCVD, HF, CKD, weight loss, MASLD), and adverse effects (hypoglycemia, gastrointestinal, other contraindications/cautions). The information selected for each medication is intended to provide a framework for clinicians to select from multiple available glucose-lowering medications and to incorporate the highlighted benefits or cautions in shared decision making with patients. Further details regarding the mechanisms of action and evidence of benefits or harms are outside the scope of this algorithm; clinicians are encouraged to consult drug monographs/inserts and the 2022 AACE Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan[10] for more details.

Algorithm 10. Profiles of Pharmacotherapy for Obesity

The table in Algorithm Fig. 10 provides an overview of weight loss medications that have regulatory approval by the FDA.[14,92,359-369] The table is intended to be a convenient resource for information about percent of weight loss (with and without T2D), A1C reduction (when applicable), mechanisms of action, dosing, and titration. Key adverse effects, cautions, and contraindications are included as a reminder, but clinicians should consult the monograph/insert of each drug for more details. The clinician is referred to the 2025 AACE Consensus Statement: Algorithm for the Treatment of Obesity/Adiposity-Based Chronic Disease for additional evidence supporting the use of these medications and for details on the comprehensive management of individuals with obesity, prediabetes, or T2D.[11]

Algorithm 11. Vaccine Recommendations for Adults With Diabetes Mellitus

Vaccine-preventable illnesses caused by bacteria and viruses result in significant morbidity and mortality, with worse outcomes among high-risk populations, including adults with DM.[370-372] Vaccinations are effective in reducing the severity and associated morbidity and mortality related to these diseases.[370,373] Despite the evidence supporting effectiveness of vaccinations among those with DM, rates of vaccination are suboptimal.[374] Clinicians may not routinely evaluate the vaccination status of their patients with DM, who are reliant on their recommendations.[375] This results in missed opportunities to increase utilization of preventive vaccines.

To address this gap in care, the CDC Advisory Committee on Immunization Practices (ACIP) developed the Standards for Adult Immunization Practice.[376] CDC/ACIP has provided a series of steps that form a framework for implementing vaccinations in the clinical setting.[377] These steps, summarized below, recognize that many health care professionals (HCPs) may not routinely prescribe or administer vaccines, but they can still play a significant role in getting patients vaccinated.

1. Assess the immunization status of all individuals with DM at every encounter. This involves keeping current on the latest vaccine recommendations, implementing protocols that facilitate review of a person's immunization status by the care team, and sending reminders for vaccinations.[378]
2. Strongly recommend the appropriate vaccines to those who are not fully vaccinated. A recommendation from an HCP is a strong predictor of a person's vaccine acceptance.[379] Explain the benefits of vaccinations, address questions and concerns, and highlight positive experiences with vaccinations.
3. Administer the vaccines you stock and, for those you do not stock, refer individuals to facilities that can provide those vaccines. Know the local resources where you can refer patients for vaccination.
4. Document vaccines administered in your office or by other vaccine providers in the electronic health record. Ensure that the electronic health record communicates with your state's immunization information system in a bidirectional manner to consolidate vaccination records. Documentation ensures that individuals get the vaccinations they need and prevents unnecessary vaccinations.

When incorporated into routine clinic visits, these steps can be effective to increase vaccination rates and provide protection for adults with DM. Having properly trained staff and a culture of vaccine confidence in the clinical practice are important in ensuring that all health care team members are engaged in efforts to improve vaccination rates. Other measures recommended to improve vaccination rates include increasing the convenience of vaccinations, coadministration of compatible vaccines, and making use of vaccination champions in the clinical setting.[380]

Review Process

Drafts of this consensus statement were reviewed and approved by all task force members, the AACE Clinical Practice Guidelines Oversight Committee, the AACE Board of Directors, and peer reviewers for *Endocrine Practice*.

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Panel Composition

This consensus statement was developed by a task force of credentialed medical professionals in the field of endocrinology who are AACE members in good standing.

Disclosures

The task force was empaneled in accordance with the 2023 AACE Conflicts of Interest Policy. Disclosures were updated and

reviewed annually at a minimum and as necessary to maintain accuracy. See Appendix A for a full list of disclosures.

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AACE reviews and considers updating or retiring its clinical guidance documents every 5 years following publication or sooner if significant scientific developments or change in public policy occurs.

References

1. Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract*. 2009;15(6):540–559. https://doi.org/10.4158/ep.15.6.540.
2. Jellinger PS, Davidson JA, Blonde L, et al. Road maps to achieve glycemic control in type 2 diabetes mellitus: ACE/AACE Diabetes Road Map Task Force. *Endocr Pract*. 2007;13(3):260–268. https://doi.org/10.4158/ep.13.3.260.
3. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm 2013. *Endocr Pract*. 2013;19(2):327–336. https://doi.org/10.4158/endp.19.2.a38267720403k242.
4. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm–2015 executive summary. *Endocr Pract*. 2015;21(12):1403–1414. https://doi.org/10.4158/ep151063.Cs.
5. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm–2016 executive summary. *Endocr Pract*. 2016;22(1):84–113. https://doi.org/10.4158/ep151126.Cs.
6. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2018 executive summary. *Endocr Pract*. 2018;24(1):91–120. https://doi.org/10.4158/cs-2017-0153.
7. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2019 executive summary. *Endocr Pract*. 2019;25(1):69–100. https://doi.org/10.4158/cs-2018-0535.
8. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2020 executive summary. *Endocr Pract*. 2020;26(1):107–139. https://doi.org/10.4158/cs-2019-0472.
9. Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology consensus statement: comprehensive type 2 diabetes management algorithm - 2023 update. *Endocr Pract*. 2023;29(5):305–340. https://doi.org/10.1016/j.eprac.2023.02.001.
10. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology clinical practice guideline: developing a diabetes mellitus comprehensive care plan-2022 update. *Endocr Pract*. 2022;28(10):923–1049. https://doi.org/10.1016/j.eprac.2022.08.002.
11. Nadolsky K, Garvey WT, Agarwal M, et al. American Association of Clinical Endocrinology consensus statement: algorithm for the evaluation and treatment of adults with obesity/adiposity-based chronic disease - 2025 update. *Endocr Pract*. 2025;31(11):1351–1394. https://doi.org/10.1016/j.eprac.2025.07.017.
12. Patel SB, Belalcazar LM, Afreen S, et al. American Association of Clinical Endocrinology consensus statement: algorithm for management of adults with dyslipidemia - 2025 update. *Endocrine Pract*. 2025;31(10):1207–1238. https://doi.org/10.1016/j.eprac.2025.07.014.
13. Patel SB, Wyne KL, Afreen S, et al. American Association of Clinical Endocrinology clinical practice guideline on pharmacologic management of adults with dyslipidemia. *Endocr Pract*. 2025;31(2):236–262. https://doi.org/10.1016/j.eprac.2024.09.016.
14. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2023;402(10402):613–626. https://doi.org/10.1016/s0140-6736(23)01200-x.
15. Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. *N Engl J Med*. 2024;391(13):1193–1205. https://doi.org/10.1056/NEJMoa2404881.
16. Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. *N Engl J Med*. 2024;390(15):1394–1407. https://doi.org/10.1056/NEJMoa2313917.
17. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. *N Engl J Med*. 2025;392(5):427–437. https://doi.org/10.1056/NEJMoa2410027.
18. Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med*. 2024;391(2):109–121. https://doi.org/10.1056/NEJMoa2403347.
19. McGuire DK, Marx N, Mulvagh SL, et al. Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. *N Engl J Med*. 2025;392(20):2001–2012. https://doi.org/10.1056/NEJMoa2501006.
20. Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med*. 2025;392(21):2089–2099. https://doi.org/10.1056/NEJMoa2413258.
21. Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med*. 2024;391(4):299–310. https://doi.org/10.1056/NEJMoa2401943.
22. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2022;45(11):2753–2786. https://doi.org/10.2337/dci22-0034.
23. Handelsman Y, Anderson JE, Bakris GL, et al. DCRM multispecialty practice recommendations for the management of diabetes, cardiorenal, and metabolic diseases. *J Diabetes Complications*. 2022;36(2):108101. https://doi.org/10.1016/j.jdiacomp.2021.108101.
24. Poole L, Hackett RA. Diabetes distress: the psychological burden of living with diabetes. *Lancet Diabetes Endocrinol*. 2024;12(7):439–441. https://doi.org/10.1016/s2213-8587(24)00126-8.
25. Nadolsky K, Addison B, Agarwal M, et al. American Association of Clinical Endocrinology Consensus Statement: addressing stigma and bias in the diagnosis and management of patients with obesity/adiposity-based chronic disease and assessing bias and stigmatization as determinants of disease severity. *Endocr Pract*. 2023;29(6):417–427. https://doi.org/10.1016/j.eprac.2023.03.272.
26. Mechanick JI, Hurley DL, Garvey WT. Adiposity-based chronic disease as a new diagnostic term: the American Association of Clinical Endocrinologists and American College of Endocrinology position statement. *Endocr Pract*. 2017;23(3):372–378. https://doi.org/10.4158/ep161688.Ps.
27. Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol*. 2025;13(3):221–262. https://doi.org/10.1016/s2213-8587(24)00316-4.
28. Garvey WT. New horizons. A new paradigm for treating to target with second-generation obesity medications. *J Clin Endocrinol Metab*. 2022;107(4):e1339–e1347. https://doi.org/10.1210/clinem/dgab848.
29. Campbell L, Pepper T, Shipman K. HbA1c: a review of non-glycaemic variables. *J Clin Pathol*. 2019;72(1):12–19. https://doi.org/10.1136/jclinpath-2017-204755.
30. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care*. 2019;42(3):400–405. https://doi.org/10.2337/dc18-1444.
31. Lu J, Ma X, Zhou J, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. *Diabetes Care*. 2018;41(11):2370–2376. https://doi.org/10.2337/dc18-1131.
32. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. *Diabetes Care*. 2019;42(8):1593–1603. https://doi.org/10.2337/dci19-0028.

33. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. 2017;40(12):1631–1640. https://doi.org/10.2337/dc17-1600.
34. Rama Chandran S, Tay WL, Lye WK, et al. Beyond HbA1c: comparing glycemic variability and glycemic indices in predicting hypoglycemia in type 1 and type 2 diabetes. *Diabetes Technol Ther*. 2018;20(5):353–362. https://doi.org/10.1089/dia.2017.0388.
35. American Diabetes Association Professional Practice Committee. 6. Glycemic goals and hypoglycemia: standards of care in diabetes-2025. *Diabetes Care*. 2025;48(1 Suppl 1):S128–S145. https://doi.org/10.2337/dc25-S006.
36. Monnier L, Colette C, Wojtusciszyn A, et al. Toward defining the threshold between low and high glucose variability in diabetes. *Diabetes Care*. 2017;40(7):832–838. https://doi.org/10.2337/dc16-1769.
37. Jin SM, Kim TH, Bae JC, et al. Clinical factors associated with absolute and relative measures of glycemic variability determined by continuous glucose monitoring: an analysis of 480 subjects. *Diabetes Res Clin Pract*. 2014;104(2):266–272. https://doi.org/10.1016/j.diabres.2014.02.003.
38. Mo Y, Ma X, Lu J, et al. Defining the target value of the coefficient of variation by continuous glucose monitoring in Chinese people with diabetes. *J Diabetes Investig*. 2021;12(6):1025–1034. https://doi.org/10.1111/jdi.13453.
39. Gómez AM, Muñoz OM, Marin A, et al. Different indexes of glycemic variability as identifiers of patients with risk of hypoglycemia in type 2 diabetes mellitus. *J Diabetes Sci Technol*. 2018;12(5):1007–1015. https://doi.org/10.1177/1932296818758105.
40. Vigersky RA, McMahon C. The relationship of hemoglobin A1c to time-in-range in patients with diabetes. *Diabetes Technol Ther*. 2019;21(2):81–85. https://doi.org/10.1089/dia.2018.0310.
41. Beck RW, Bergenstal RM, Cheng P, et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. *J Diabetes Sci Technol*. 2019;13(4):614–626. https://doi.org/10.1177/1932296818822496.
42. Grunberger G, Sherr J, Allende M, et al. American Association of Clinical Endocrinology clinical practice guideline: the use of advanced technology in the management of persons with diabetes mellitus. *Endocr Pract*. 2021;27(6):505–537. https://doi.org/10.1016/j.eprac.2021.04.008.
43. Bergenstal RM, Beck RW, Close KL, et al. Glucose management indicator (GMI): a new term for estimating A1C from continuous glucose monitoring. *Diabetes Care*. 2018;41(11):2275–2280. https://doi.org/10.2337/dc18-1581.
44. Perlman JE, Gooley TA, McNulty B, Meyers J, Hirsch IB. HbA1c and glucose management indicator discordance: a real-world analysis. *Diabetes Technol Ther*. 2021;23(4):253–258. https://doi.org/10.1089/dia.2020.0501.
45. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet*. 2010;376(9739):419–430. https://doi.org/10.1016/s0140-6736(10)60576-4.
46. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560–2572. https://doi.org/10.1056/NEJMoa0802987.
47. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545–2559. https://doi.org/10.1056/NEJMoa0802743.
48. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med*. 2004;141(6):413–420. https://doi.org/10.7326/0003-4819-141-6-200409210-00006.
49. Rodriguez-Gutierrez R, Gonzalez-Gonzalez JG, Zuñiga-Hernandez JA, McCoy RG. Benefits and harms of intensive glycemic control in patients with type 2 diabetes. *BMJ*. 2019;367:l5887. https://doi.org/10.1136/bmj.l5887.
50. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360(2):129–139. https://doi.org/10.1056/NEJMoa0808431.
51. Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. *Ann Intern Med*. 2011;154(8):554–559. https://doi.org/10.7326/0003-4819-154-8-201104190-00007.
52. Powell RE, Zaccardi F, Beebe C, et al. Strategies for overcoming therapeutic inertia in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2021;23(9):2137–2154. https://doi.org/10.1111/dom.14455.
53. Khunti K, Gomes MB, Pocock S, et al. Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: a systematic review. *Diabetes Obes Metab*. 2018;20(2):427–437. https://doi.org/10.1111/dom.13088.
54. Chalmers J, Cooper ME. UKPDS and the legacy effect. *N Engl J Med*. 2008;359(15):1618–1620. https://doi.org/10.1056/NEJMe0807625.
55. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577–1589. https://doi.org/10.1056/NEJMoa0806470.
56. Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (The Diabetes & Aging Study). *Diabetes Care*. 2019;42(3):416–426. https://doi.org/10.2337/dc17-1144.
57. Martens T, Beck RW, Bailey R, et al. Effect of continuous glucose monitoring on glycemic control in patients with type 2 diabetes treated with basal insulin: a randomized clinical trial. *JAMA*. 2021;325(22):2262–2272. https://doi.org/10.1001/jama.2021.7444.
58. Karter AJ, Parker MM, Moffet HH, Gilliam LK, Dlott R. Association of real-time continuous glucose monitoring with glycemic control and acute metabolic events among patients with insulin-treated diabetes. *JAMA*. 2021;325(22):2273–2284. https://doi.org/10.1001/jama.2021.6530.
59. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. *Diabetes Ther*. 2017;8(1):55–73. https://doi.org/10.1007/s13300-016-0223-6.
60. Jancev M, Vissers T, Visseren FLJ, et al. Continuous glucose monitoring in adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetologia*. 2024;67(5):798–810. https://doi.org/10.1007/s00125-024-06107-6.
61. Ehrhardt N, Al Zaghal E. Behavior modification in prediabetes and diabetes: potential use of real-time continuous glucose monitoring. *J Diabetes Sci Technol*. 2019;13(2):271–275. https://doi.org/10.1177/1932296818790994.
62. Clark TL, Polonsky WH, Soriano EC. The potential impact of continuous glucose monitoring use on diabetes-related attitudes and behaviors in adults with type 2 diabetes: a qualitative investigation of the patient experience. *Diabetes Technol Ther*. 2024;26(10):700–708. https://doi.org/10.1089/dia.2023.0612.
63. Yoo HJ, An HG, Park SY, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. *Diabetes Res Clin Pract*. 2008;82(1):73–79. https://doi.org/10.1016/j.diabres.2008.06.015.
64. Ettestad TM, Willis HJ, Johnson E, Green CR, Bergenstal RM. Continuous glucose monitoring (CGM) as a behavior modification tool: a case series on CGM-guided nutrition in people with type 2 diabetes not using insulin. *Clin Diabetes*. 2025;43(4):610–617. https://doi.org/10.2337/cd24-0106.
65. Allen NA, Fain JA, Braun B, Chipkin SR. Continuous glucose monitoring counseling improves physical activity behaviors of individuals with type 2 diabetes: a randomized clinical trial. *Diabetes Res Clin Pract*. 2008;80(3):371–379. https://doi.org/10.1016/j.diabres.2008.01.006.
66. Cox DJ, Taylor AG, Moncrief M, et al. Continuous glucose monitoring in the self-management of type 2 diabetes: a paradigm shift. *Diabetes Care*. 2016;39(5):e71–e73. https://doi.org/10.2337/dc15-2836.
67. Bailey KJ, Little JP, Jung ME. Self-monitoring using continuous glucose monitors with real-time feedback improves exercise adherence in individuals with impaired blood glucose: a pilot study. *Diabetes Technol Ther*. 2016;18(3):185–193. https://doi.org/10.1089/dia.2015.0285.
68. Allen N, Whittemore R, Melkus G. A continuous glucose monitoring and problem-solving intervention to change physical activity behavior in women with type 2 diabetes: a pilot study. *Diabetes Technol Ther*. 2011;13(11):1091–1099. https://doi.org/10.1089/dia.2011.0088.
69. Bethel MA, Hyland KA, Chacra AR, et al. Updated risk factors should be used to predict development of diabetes. *J Diabetes Complications*. 2017;31(5):859–863. https://doi.org/10.1016/j.jdiacomp.2017.02.012.
70. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143–3421.
71. de Vegt F, Dekker JM, Jager A, et al. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: the Hoorn study. *JAMA*. 2001;285(16):2109–2113. https://doi.org/10.1001/jama.285.16.2109.
72. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288(21):2709–2716. https://doi.org/10.1001/jama.288.21.2709.
73. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am J Epidemiol*. 2002;156(11):1070–1077. https://doi.org/10.1093/aje/kwf145.
74. Liu Y, Li J, Wu Y, et al. Evidence from a systematic review and meta-analysis: classical impaired glucose tolerance should be divided into subgroups of isolated impaired glucose tolerance and impaired glucose tolerance combined with impaired fasting glucose, according to the risk of progression to diabetes. *Front Endocrinol (Lausanne)*. 2022;13:835460. https://doi.org/10.3389/fendo.2022.835460.
75. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393–403. https://doi.org/10.1056/NEJMoa012512.
76. Laaksonen DE, Lindström J, Lakka TA, et al. Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study. *Diabetes*. 2005;54(1):158–165. https://doi.org/10.2337/diabetes.54.1.158.
77. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997;20(4):537–544. https://doi.org/10.2337/diacare.20.4.537.
78. Salas-Salvadó J, Bulló M, Estruch R, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Ann Intern Med*. 2014;160(1):1–10. https://doi.org/10.7326/m13-1725.

79. Salas-Salvadó J, Bulló M, Babio N, et al. Erratum. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care*. 2011;34:14–19. *Diabetes Care*. 2018;41(10):2259-2260 https://doi.org/10.2337/dc18-er10.
80. Svetkey LP, Simons-Morton D, Vollmer WM, et al. Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Arch Intern Med*. 1999;159(3):285–293. https://doi.org/10.1001/archinte.159.3.285.
81. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;344(1):3–10. https://doi.org/10.1056/nejm200101043440101.
82. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. *Diabetes Care*. 2010;33(12):2692–2696. https://doi.org/10.2337/dc10-1548.
83. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care*. 2010;33(12):e147–e167. https://doi.org/10.2337/dc10-9990.
84. Dai X, Zhai L, Chen Q, et al. Two-year-supervised resistance training prevented diabetes incidence in people with prediabetes: a randomised control trial. *Diabetes Metab Res Rev*. 2019;35(5):e3143. https://doi.org/10.1002/dmrr.3143.
85. Aguiar EJ, Morgan PJ, Collins CE, Plotnikoff RC, Callister R. Efficacy of interventions that include diet, aerobic and resistance training components for type 2 diabetes prevention: a systematic review with meta-analysis. *Int J Behav Nutr Phys Act*. 2014;11:2. https://doi.org/10.1186/1479-5868-11-2.
86. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2960–2984. https://doi.org/10.1016/j.jacc.2013.11.003.
87. Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care*. 2014;37(4):912–921. https://doi.org/10.2337/dc13-1518.
88. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989–1002. https://doi.org/10.1056/NEJMoa2032183.
89. Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA*. 2021;325(14):1403–1413. https://doi.org/10.1001/jama.2021.1831.
90. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA*. 2021;325(14):1414–1425. https://doi.org/10.1001/jama.2021.3224.
91. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. 2017;389(10077):1399–1409. https://doi.org/10.1016/s0140-6736(17)30069-7.
92. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205–216. https://doi.org/10.1056/NEJMoa2206038.
93. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389(24):2221–2232. https://doi.org/10.1056/NEJMoa2307563.
94. Greenway FL, Aronne LJ, Raben A, et al. A randomized, double-blind, placebo-controlled study of Gelesis100: a novel nonsystemic oral hydrogel for weight loss. *Obesity (Silver Spring)*. 2019;27(2):205–216. https://doi.org/10.1002/oby.22347.
95. Genco A, Bruni T, Doldi SB, et al. BioEnterics intragastric balloon: the Italian experience with 2,515 patients. *Obes Surg*. 2005;15(8):1161–1164. https://doi.org/10.1381/0960892055002202.
96. Ponce J, Woodman G, Swain J, et al. The REDUCE pivotal trial: a prospective, randomized controlled pivotal trial of a dual intragastric balloon for the treatment of obesity. *Surg Obes Relat Dis*. 2015;11(4):874–881. https://doi.org/10.1016/j.soard.2014.12.006.
97. Marinos G, Eliades C, Raman Muthusamy V, Greenway F. Weight loss and improved quality of life with a nonsurgical endoscopic treatment for obesity: clinical results from a 3- and 6-month study. *Surg Obes Relat Dis*. 2014;10(5):929–934. https://doi.org/10.1016/j.soard.2014.03.005.
98. Mechanick JI, Apovian C, Brethauer S, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/ American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists - Executive summary. *Endocr Pract*. 2019;25(12):1346–1359. https://doi.org/10.4158/gl-2019-0406.
99. Eisenberg D, Shikora SA, Aarts E, et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): indications for metabolic and bariatric surgery. *Surg Obes Relat Dis*. 2022;18(12):1345–1356. https://doi.org/10.1016/j.soard.2022.08.013.
100. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359(9323):2072–2077. https://doi.org/10.1016/s0140-6736(02)08905-5.
101. DeFronzo RA, Tripathy D, Schwenke DC, et al. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med*. 2011;364(12):1104–1115. https://doi.org/10.1056/NEJMoa1010949.
102. Phillip M, Achenbach P, Addala A, et al. Consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes. *Diabetes Care*. 2024;47(8):1276–1298. https://doi.org/10.2337/dci24-0042.
103. Fellinger P, Fuchs D, Wolf P, et al. Overweight and obesity in type 1 diabetes equal those of the general population. *Wien Klin Wochenschr*. 2019;131(3-4):55–60. https://doi.org/10.1007/s00508-018-1434-9.
104. Donga E, Dekkers OM, Corssmit EP, Romijn JA. Insulin resistance in patients with type 1 diabetes assessed by glucose clamp studies: systematic review and meta-analysis. *Eur J Endocrinol*. 2015;173(1):101–109. https://doi.org/10.1530/eje-14-0911.
105. Thomas NJ, Lynam AL, Hill AV, et al. Type 1 diabetes defined by severe insulin deficiency occurs after 30 years of age and is commonly treated as type 2 diabetes. *Diabetologia*. 2019;62(7):1167–1172. https://doi.org/10.1007/s00125-019-4863-8.
106. Muñoz C, Floreen A, Garey C, et al. Misdiagnosis and diabetic ketoacidosis at diagnosis of type 1 diabetes: patient and caregiver perspectives. *Clin Diabetes*. 2019;37(3):276–281. https://doi.org/10.2337/cd18-0088.
107. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes-2025. *Diabetes Care*. 2025;48(Suppl 1):S27–S49. https://doi.org/10.2337/dc25-S002.
108. Hsu WC, Araneta MR, Kanaya AM, Chiang JL, Fujimoto W. BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. *Diabetes Care*. 2015;38(1):150–158. https://doi.org/10.2337/dc14-2391.
109. Choo V. WHO reassesses appropriate body-mass index for Asian populations. *Lancet*. 2002;360(9328):235. https://doi.org/10.1016/s0140-6736(02)09512-0.
110. Goda A, Masuyama T. Obesity and overweight in Asian people. *Circ J*. 2016;80(12):2425–2426. https://doi.org/10.1253/circj.CJ-16-1087.
111. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(Suppl 3):1–203. https://doi.org/10.4158/ep161365.GI.
112. Zhu Y, Sidell MA, Arterburn D, et al. Racial/ethnic disparities in the prevalence of diabetes and prediabetes by BMI: patient outcomes research to advance learning (PORTAL) multisite cohort of adults in the U.S. *Diabetes Care*. 2019;42(12):2211–2219. https://doi.org/10.2337/dc19-0532.
113. Eckel N, Mühlenbruch K, Meidtner K, Boeing H, Stefan N, Schulze MB. Characterization of metabolically unhealthy normal-weight individuals: risk factors and their associations with type 2 diabetes. *Metabolism*. 2015;64(8):862–871. https://doi.org/10.1016/j.metabol.2015.03.009.
114. Leslie RD, Evans-Molina C, Freund-Brown J, et al. Adult-onset type 1 diabetes: current understanding and challenges. *Diabetes Care*. 2021;44(11):2449–2456. https://doi.org/10.2337/dc21-0770.
115. Fang M, Wang D, Echouffo-Tcheugui JB, Selvin E. Age at diagnosis in U.S. adults with type 1 diabetes. *Ann Intern Med*. 2023;176(11):1567–1568. https://doi.org/10.7326/m23-1707.
116. Gregory GA, Robinson TIG, Linklater SE, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. *Lancet Diabetes Endocrinol*. 2022;10(10):741–760. https://doi.org/10.1016/s2213-8587(22)00218-2.
117. Buzzetti R, Tuomi T, Mauricio D, et al. Management of latent autoimmune diabetes in adults: a consensus statement from an international expert panel. *Diabetes*. 2020;69(10):2037–2047. https://doi.org/10.2337/dbi20-0017.
118. Hernández M, Mauricio D. Latent autoimmune diabetes in adults: a review of clinically relevant issues. *Adv Exp Med Biol*. 2021;1307:29–41. https://doi.org/10.1007/5584_2020_533.
119. Yin W, Luo S, Xiao Z, Zhang Z, Liu B, Zhou Z. Latent autoimmune diabetes in adults: a focus on β-cell protection and therapy. *Front Endocrinol (Lausanne)*. 2022;13:959011. https://doi.org/10.3389/fendo.2022.959011.
120. Leichter SB, Felton JL, Geno Rasmussen C, et al. Establishing screening programs for presymptomatic type 1 diabetes: practical guidance for diabetes care providers. *J Clin Endocrinol Metab*. 2025;110(8):2371–2382. https://doi.org/10.1210/clinem/dgaf194.
121. Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: ketosis-prone type 2 diabetes mellitus. *Ann Intern Med*. 2006;144(5):350–357. https://doi.org/10.7326/0003-4819-144-5-200603070-00011.
122. Gaba R, Mehta P, Balasubramanyam A. Evaluation and management of ketosis-prone diabetes. *Expert Rev Endocrinol Metab*. 2019;14(1):43–48. https://doi.org/10.1080/17446651.2019.1561270.
123. Balasubramanyam A. Syndromes of ketosis-prone diabetes. *Trans Am Clin Climatol Assoc*. 2019;130:145–155.
124. Karjalainen J, Salmela P, Ilonen J, Surcel HM, Knip M. A comparison of childhood and adult type I diabetes mellitus. *N Engl J Med*. 1989;320(14):881–886. https://doi.org/10.1056/nejm198904063201401.

125. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. *Diabet Med*. 2013;30(7):803–817. https://doi.org/10.1111/dme.12159.
126. Patel SK, Ma CS, Fourlanos S, Greenfield JR. Autoantibody-negative type 1 diabetes: a neglected subtype. *Trends Endocrinol Metab*. 2021;32(5):295–305. https://doi.org/10.1016/j.tem.2021.02.001.
127. Iqbal S, Jayyab AA, Alrashdi AM, Reverté-Villarroya S. The predictive ability of C-peptide in distinguishing type 1 diabetes from type 2 diabetes: a systematic review and meta-analysis. *Endocr Pract*. 2023;29(5):379–387. https://doi.org/10.1016/j.eprac.2023.01.004.
128. Schleicher E, Kabytaev K, Nauck M, et al. Call for standardization of C-peptide measurement. *J Diabetes Sci Technol*. Posted online Aug 8. Accessed •••. https://doi.org/10.1177/19322968251362848
129. Greenbaum CJ, Mandrup-Poulsen T, McGee PF, et al. Mixed-meal tolerance test versus glucagon stimulation test for the assessment of beta-cell function in therapeutic trials in type 1 diabetes. *Diabetes Care*. 2008;31(10):1966–1971. https://doi.org/10.2337/dc07-2451.
130. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2021;64(12):2609–2652. https://doi.org/10.1007/s00125-021-05568-3.
131. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2021;44(11):2589–2625. https://doi.org/10.2337/dci21-0043.
132. Giordano R, Picu A, Marinazzo E, et al. Metabolic and cardiovascular outcomes in patients with Cushing's syndrome of different aetiologies during active disease and 1 year after remission. *Clin Endocrinol (Oxf)*. 2011;75(3):354–360. https://doi.org/10.1111/j.1365-2265.2011.04055.x.
133. Samson SL. Is diabetes with acromegaly for life? *Pituitary*. 2024;27(5):433–436. https://doi.org/10.1007/s11102-024-01438-4.
134. Pascual-Corrales E, Biagetti B, Marazuela M, et al. Glucose metabolism outcomes after pituitary surgery in patients with acromegaly. *Pituitary*. 2024;27(5):497–506. https://doi.org/10.1007/s11102-024-01415-x.
135. Biagetti B, Araujo-Castro M, Marazuela M, Puig-Domingo M. Treatment of acromegaly-induced diabetes: an updated proposal. *Pituitary*. 2024;28(1):15. https://doi.org/10.1007/s11102-024-01477-x.
136. Esposito D, Boguszewski CL, Colao A, et al. Diabetes mellitus in patients with acromegaly: pathophysiology, clinical challenges and management. *Nat Rev Endocrinol*. 2024;20(9):541–552. https://doi.org/10.1038/s41574-024-00993-x.
137. Findling JW, Raff H. Cushing's syndrome: important issues in diagnosis and management. *J Clin Endocrinol Metab*. 2006;91(10):3746–3753. https://doi.org/10.1210/jc.2006-0997.
138. Buse JB, Kahn SE, Aroda VR, et al. Prevalence of hypercortisolism in difficult-to-control type 2 diabetes. *Diabetes Care*. 2025;48(12):2012–2020. https://doi.org/10.2337/dc24-2841.
139. DeFronzo RA, Fonseca V, Aroda VR, et al. Inadequately controlled type 2 diabetes and hypercortisolism: improved glycemia with mifepristone treatment. *Diabetes Care*. 2025;48(12):2036–2044. https://doi.org/10.2337/dc25-1055.
140. Charitou MM, Al-Bahadili H. Type 3c diabetes. In: Schulman-Rosenbaum RC, ed. *Diabetes Management in Hospitalized Patients*. Springer Cham; 2023:207–216.
141. Kayani K, Mohammed R, Mohiaddin H. Cystic fibrosis-related diabetes. *Front Endocrinol (Lausanne)*. 2018;9:20. https://doi.org/10.3389/fendo.2018.00020.
142. Richstein R, Menon T, Wang J. Cystic fibrosis-related diabetes. In: Schulman-Rosenbaum RC, ed. *Diabetes Management in Hospitalized Patients*. Springer Cham; 2023:217–234.
143. Laver TW, Patel KA. Maturity onset diabetes of the young and beyond: the changing face of single-gene diabetes. *Eur J Endocrinol*. 2025;193(3):R25–R29. https://doi.org/10.1093/ejendo/lvaf172.
144. Delvecchio M, Pastore C, Giordano P. Treatment options for MODY patients: a systematic review of literature. *Diabetes Ther*. 2020;11(8):1667–1685. https://doi.org/10.1007/s13300-020-00864-4.
145. Ershadinia N, Tritos NA. Diagnosis and treatment of acromegaly: an update. *Mayo Clin Proc*. 2022;97(2):333–346. https://doi.org/10.1016/j.mayocp.2021.11.007.
146. Exeter Diabetes. MODY calculator. https://www.diabetesgenes.org/exeter-diabetes-app/. Accessed January 8, 2025.
147. Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. *Diabetologia*. 2012;55(5):1265–1272. https://doi.org/10.1007/s00125-011-2418-8.
148. Brooks D, Schulman-Rosenbaum R, Griff M, Lester J, Low Wang CC. Glucocorticoid-induced hyperglycemia including dexamethasone-associated hyperglycemia in COVID-19 infection: a systematic review. *Endocr Pract*. 2022;28(11):1166–1177. https://doi.org/10.1016/j.eprac.2022.07.014.
149. Triñanes J, Ten Dijke P, Groen N, et al. Tacrolimus-induced BMP/SMAD signaling associates with metabolic stress-activated FOXO1 to trigger β-cell failure. *Diabetes*. 2020;69(2):193–204. https://doi.org/10.2337/db19-0828.
150. Lombardi A, Trimarco B, Iaccarino G, Santulli G. Impaired mitochondrial calcium uptake caused by tacrolimus underlies beta-cell failure. *Cell Commun Signal*. 2017;15(1):47. https://doi.org/10.1186/s12964-017-0203-0.
151. Kanbay M, Copur S, Topçu AU, et al. An update review of post-transplant diabetes mellitus: concept, risk factors, clinical implications and management. *Diabetes Obes Metab*. 2024;26(7):2531–2545. https://doi.org/10.1111/dom.15575.
152. Li Z, Sun F, Zhang Y, et al. Tacrolimus induces insulin resistance and increases the glucose absorption in the jejunum: a potential mechanism of the diabetogenic effects. *PLoS One*. 2015;10(11):e0143405. https://doi.org/10.1371/journal.pone.0143405.
153. Yuen KCJ, Samson SL, Bancos I, et al. American Association of Clinical Endocrinology disease state clinical review: evaluation and management of immune checkpoint inhibitor-mediated endocrinopathies: a practical case-based clinical approach. *Endocr Pract*. 2022;28(7):719–731. https://doi.org/10.1016/j.eprac.2022.04.010.
154. Wu L, Carlino MS, Brown DA, et al. Checkpoint inhibitor-associated autoimmune diabetes mellitus is characterized by C-peptide loss and pancreatic atrophy. *J Clin Endocrinol Metab*. 2024;109(5):1301–1307. https://doi.org/10.1210/clinem/dgad685.
155. Maassen JA, LM TH, Van Essen E, et al. Mitochondrial diabetes: molecular mechanisms and clinical presentation. *Diabetes*. 2004;53(Suppl 1):S103–S109. https://doi.org/10.2337/diabetes.53.2007.s103.
156. Patni N, Garg A. Lipodystrophy for the diabetologist-what to look for. *Curr Diab Rep*. 2022;22(9):461–470. https://doi.org/10.1007/s11892-022-01485-w.
157. Flores-Le Roux JA, Comin J, Pedro-Botet J, et al. Seven-year mortality in heart failure patients with undiagnosed diabetes: an observational study. *Cardiovasc Diabetol*. 2011;10:39. https://doi.org/10.1186/1475-2840-10-39.
158. Giraldez RR, Clare RM, Lopes RD, et al. Prevalence and clinical outcomes of undiagnosed diabetes mellitus and prediabetes among patients with high-risk non-ST-segment elevation acute coronary syndrome. *Am Heart J*. 2013;165(6):918–925.e2. https://doi.org/10.1016/j.ahj.2013.01.005.
159. Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet*. 2002;359(9324):2140–2144. https://doi.org/10.1016/s0140-6736(02)09089-x.
160. Wang N, Fulcher J, Abeysuriya N, et al. Intensive LDL cholesterol-lowering treatment beyond current recommendations for the prevention of major vascular events: a systematic review and meta-analysis of randomised trials including 327 037 participants. *Lancet Diabetes Endocrinol*. 2020;8(1):36–49. https://doi.org/10.1016/s2213-8587(19)30388-2.
161. de Ritter R, Sep SJS, van der Kallen CJH, et al. Adverse differences in cardiometabolic risk factor levels between individuals with pre-diabetes and normal glucose metabolism are more pronounced in women than in men: the Maastricht Study. *BMJ Open Diabetes Res Care*. 2019;7(1):e000787. https://doi.org/10.1136/bmjdrc-2019-000787.
162. Hashemi Madani N, Ismail-Beigi F, Poustchi H, et al. Impaired fasting glucose and major adverse cardiovascular events by hypertension and dyslipidemia status: the Golestan cohort study. *BMC Cardiovasc Disord*. 2020;20(1):113. https://doi.org/10.1186/s12872-020-01390-8.
163. Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia*. 2003;46(6):733–749. https://doi.org/10.1007/s00125-003-1111-y.
164. Halcox JP, Banegas JR, Roy C, et al. Prevalence and treatment of atherogenic dyslipidemia in the primary prevention of cardiovascular disease in Europe: EURIKA, a cross-sectional observational study. *BMC Cardiovasc Disord*. 2017;17(1):160. https://doi.org/10.1186/s12872-017-0591-5.
165. Jin JL, Zhang HW, Cao YX, et al. Association of small dense low-density lipoprotein with cardiovascular outcome in patients with coronary artery disease and diabetes: a prospective, observational cohort study. *Cardiovasc Diabetol*. 2020;19(1):45. https://doi.org/10.1186/s12933-020-01015-6.
166. Mora S, Chang CL, Moorthy MV, Sever PS. Association of nonfasting vs fasting lipid levels with risk of major coronary events in the anglo-scandinavian cardiac outcomes trial-lipid lowering arm. *JAMA Intern Med*. 2019;179(7):898–905. https://doi.org/10.1001/jamainternmed.2019.0392.
167. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*. 2011;34(7):1481–1486. https://doi.org/10.2337/dc10-2415.
168. Handelsman Y, Jellinger PS, Guerin CK, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the management of dyslipidemia and prevention of cardiovascular disease algorithm - 2020 executive summary. *Endocr Pract*. 2020;26(10):1196–1224. https://doi.org/10.4158/cs-2020-0490.
169. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889–2934. https://doi.org/10.1016/j.jacc.2013.11.002.
170. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet*. 2012;380(9841):565–571. https://doi.org/10.1016/s0140-6736(12)61190-8.
171. Cholesterol Treatment Trialists' (CTT) Collaboration. Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-

analysis. *Lancet Diabetes Endocrinol*. 2024;12(5):306–319. https://doi.org/10.1016/s2213-8587(24)00040-8.
172. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305(24):2556–2564. https://doi.org/10.1001/jama.2011.860.
173. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375(9716):735–742. https://doi.org/10.1016/s0140-6736(09)61965-6.
174. Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2019;39(2):e38–e81. https://doi.org/10.1161/atv.0000000000000073.
175. No authors listed. Correction to: statin safety and associated adverse events: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2019;39(5):e158. https://doi.org/10.1161/atv.0000000000000081.
176. Qu H, Guo M, Chai H, Wang WT, Gao ZY, Shi DZ. Effects of coenzyme q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7(19):e009835. https://doi.org/10.1161/jaha.118.009835.
177. Hlatky MA, Gonzalez PE, Manson JE, et al. Statin-associated muscle symptoms among new statin users randomly assigned to vitamin D or placebo. *JAMA Cardiol*. 2023;8(1):74–80. https://doi.org/10.1001/jamacardio.2022.4250.
178. Authors/Task Force Members, ESC Committee for Practice Guidelines (CPG) ENCS. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Atherosclerosis*. 2019;290:140–205. https://doi.org/10.1016/j.atherosclerosis.2019.08.014.
179. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease - executive summary (complete appendix to guidelines available at http://journals.aace.com). *Endocr Pract*. 2017;23(4):479–497. https://doi.org/10.4158/ep171764.Gl.
180. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387–2397. https://doi.org/10.1056/NEJMoa1410489.
181. Singeisen H, Renström F, Laimer M, Lehmann R, Bilz S, Brändle M. An estimation of the consequences of reinforcing the 2016 and 2019 European Society of Cardiology/European Atherosclerosis Society guidelines on current lipid-lowering treatment in patients with type 2 diabetes in tertiary care-a SwissDiab study. *Eur J Prev Cardiol*. 2023;30(14):1473–1481. https://doi.org/10.1093/eurjpc/zwad178.
182. U.S. Food and Drug Administration. *Repatha (evolocumab) injection, for subcutaneous use*. prescribing information; Updated August 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125522s045lbl.pdf. Accessed January 7, 2026.
183. U.S. Food and Drug Administration. *Praluent (alirocumab) injection, for subcutaneous use*. prescribing information; Updated April 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125559s029s030lbl.pdf. Accessed January 7, 2026.
184. Das Pradhan A, Glynn RJ, Fruchart JC, et al. Triglyceride lowering with pemafibrate to reduce cardiovascular risk. *N Engl J Med*. 2022;387(21):1923–1934. https://doi.org/10.1056/NEJMoa2210645.
185. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1563–1574. https://doi.org/10.1056/NEJMoa1001282.
186. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract*. 2017;23(Suppl 2):1–87. https://doi.org/10.4158/ep171764.Appgl.
187. Scott R, O'Brien R, Fulcher G, et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the fenofibrate intervention and event lowering in diabetes (FIELD) study. *Diabetes Care*. 2009;32(3):493–498. https://doi.org/10.2337/dc08-1543.
188. Bruckert E, Labreuche J, Deplanque D, Touboul PJ, Amarenco P. Fibrates effect on cardiovascular risk is greater in patients with high triglyceride levels or atherogenic dyslipidemia profile: a systematic review and meta-analysis. *J Cardiovasc Pharmacol*. 2011;57(2):267–272. https://doi.org/10.1097/FJC.0b013e318202709f.
189. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. *Atherosclerosis*. 2011;217(2):492–498. https://doi.org/10.1016/j.atherosclerosis.2011.04.020.
190. Kim KA, Kim NJ, Choo EH. The effect of fibrates on lowering low-density lipoprotein cholesterol and cardiovascular risk reduction: a systemic review and meta-analysis. *Eur J Prev Cardiol*. 2024;31(3):291–301. https://doi.org/10.1093/eurjpc/zwad331.
191. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11–22. https://doi.org/10.1056/NEJMoa1812792.
192. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA*. 2020;324(22):2268–2280. https://doi.org/10.1001/jama.2020.22258.
193. Stroes ESG, Alexander VJ, Karwatowska-Prokopczuk E, et al. Olezarsen, acute pancreatitis, and familial chylomicronemia syndrome. *N Engl J Med*. 2024;390(19):1781–1792. https://doi.org/10.1056/NEJMoa2400201.
194. Suh DC, Kim CM, Choi IS, Plauschinat CA, Barone JA. Trends in blood pressure control and treatment among type 2 diabetes with comorbid hypertension in the United States: 1988-2004. *J Hypertens*. 2009;27(9):1908–1916. https://doi.org/10.1097/HJH.0b013e32832d4aee.
195. Liu HH, Cao YX, Li S, et al. Impacts of prediabetes mellitus alone or plus hypertension on the coronary severity and cardiovascular outcomes. *Hypertension*. 2018;71(6):1039–1046. https://doi.org/10.1161/hypertensionaha.118.11063.
196. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ*. 1998;317(7160):703–713.
197. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ*. 2000;321(7258):412–419. https://doi.org/10.1136/bmj.321.7258.412.
198. Guo X, Sun G, Xu Y, et al. Benefit-harm trade-offs of intensive blood pressure control versus standard blood pressure control on cardiovascular and renal outcomes: an individual participant data analysis of randomised controlled trials. *Lancet*. 2025;406(10507):1009–1019. https://doi.org/10.1016/s0140-6736(25)01391-1.
199. Liu J, Li Y, Ge J, et al. Lowering systolic blood pressure to less than 120 mm Hg versus less than 140 mm Hg in patients with high cardiovascular risk with and without diabetes or previous stroke: an open-label, blinded-outcome, randomised trial. *Lancet*. 2024;404(10449):245–255. https://doi.org/10.1016/s0140-6736(24)01028-6.
200. Li J, Lei L, Li Y, et al. Effect of intensive blood pressure control on stroke: A prespecified secondary analysis of the ESPRIT trial. *J Am Coll Cardiol*. 2025;86(17):1405–1417. https://doi.org/10.1016/j.jacc.2025.07.055.
201. Adler GK, Stowasser M, Correa RR, et al. Primary aldosteronism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2025;110(9):2453–2495. https://doi.org/10.1210/clinem/dgaf284.
202. Hu Y, Zhang J, Liu W, Su X. Determining the prevalence of primary aldosteronism in patients with new-onset type 2 diabetes and hypertension. *J Clin Endocrinol Metab*. 2020;105(4):dgz293. https://doi.org/10.1210/clinem/dgz293.
203. Murase K, Nagaishi R, Takenoshita H, Nomiyama T, Akehi Y, Yanase T. Prevalence and clinical characteristics of primary aldosteronism in Japanese patients with type 2 diabetes mellitus and hypertension. *Endocr J*. 2013;60(8):967–976. https://doi.org/10.1507/endocrj.ej13-0060.
204. Grossman E. Ambulatory blood pressure monitoring in the diagnosis and management of hypertension. *Diabetes Care*. 2013;36(Suppl 2 Suppl 2):S307–S311. https://doi.org/10.2337/dcS13-2039.
205. Pierdomenico SD, Cuccurullo F. Ambulatory blood pressure monitoring in type 2 diabetes and metabolic syndrome: a review. *Blood Press Monit*. 2010;15(1):1–7. https://doi.org/10.1097/MBP.0b013e3283360ed1.
206. Stergiou GS, Argyraki KK, Moyssakis I, et al. Home blood pressure is as reliable as ambulatory blood pressure in predicting target-organ damage in hypertension. *Am J Hypertens*. 2007;20(6):616–621. https://doi.org/10.1016/j.amjhyper.2006.12.013.
207. Parati G, Stergiou GS, Asmar R, et al. European Society of Hypertension practice guidelines for home blood pressure monitoring. *J Hum Hypertens*. 2010;24(12):779–785. https://doi.org/10.1038/jhh.2010.54.
208. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*. 2003;42(5):878–884. https://doi.org/10.1161/01.Hyp.0000094221.86888.Ae.
209. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc*. 2013;2(1):e004473. https://doi.org/10.1161/jaha.112.004473.
210. Conlin PR. The dietary approaches to stop hypertension (DASH) clinical trial: implications for lifestyle modifications in the treatment of hypertensive patients. *Cardiol Rev*. 1999;7(5):284–288. https://doi.org/10.1097/00045415-199909000-00013.
211. Jeong SY, Wee CC, Kovell LC, et al. Effects of diet on 10-year atherosclerotic cardiovascular disease risk (from the DASH Trial). *Am J Cardiol*. 2023;187:10–17. https://doi.org/10.1016/j.amjcard.2022.10.019.
212. Davis CR, Hodgson JM, Woodman R, Bryan J, Wilson C, Murphy KJ. A Mediterranean diet lowers blood pressure and improves endothelial function: results from the MedLey randomized intervention trial. *Am J Clin Nutr*. 2017;105(6):1305–1313. https://doi.org/10.3945/ajcn.116.146803.
213. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378(25):e34. https://doi.org/10.1056/NEJMoa1800389.
214. Saglimbene V, Palmer SC, Ruospo M, et al. The long-term impact of renin-angiotensin system (RAS) inhibition on cardiorenal outcomes (LIRICO): a randomized, controlled trial. *J Am Soc Nephrol*. 2018;29(12):2890–2899. https://doi.org/10.1681/asn.2018040443.

215. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369(20):1892–1903. https://doi.org/10.1056/NEJMoa1303154.
216. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet*. 2015;385(9982):2047–2056. https://doi.org/10.1016/s0140-6736(14)62459-4.
217. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547–1559. https://doi.org/10.1056/NEJMoa0801317.
218. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367(23):2204–2213. https://doi.org/10.1056/NEJMoa1208799.
219. Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2005;165(8):936–946. https://doi.org/10.1001/archinte.165.8.936.
220. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015;386(10008):2059–2068. https://doi.org/10.1016/s0140-6736(15)00257-3.
221. American Diabetes Association Professional Practice Committee. 11. Chronic kidney disease and risk management: standards of care in diabetes-2025. *Diabetes Care*. 2025;48(1 Suppl 1):S239–S251. https://doi.org/10.2337/dc25-S011.
222. U.S. Food and Drug Administration. *Aldactone (spironolactone) tablets for oral use*. prescribing information; Updated March 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/012151s075lbl.pdf. Accessed January 7, 2026.
223. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med*. 2020;383(23):2219–2229. https://doi.org/10.1056/NEJMoa2025845.
224. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J*. 2022;43(6):474–484. https://doi.org/10.1093/eurheartj/ehab777.
225. No authors listed. Corrigendum to: Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J*. 2022;43(20):1989. https://doi.org/10.1093/eurheartj/ehab886.
226. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med*. 2021;385(24):2252–2263. https://doi.org/10.1056/NEJMoa2110956.
227. U.S. Food and Drug Administration. Kerendia (finerenone tablets), for oral use, prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215341s000lbl.pdf; Updated July 2021. Accessed January 7, 2026.
228. Pischon T, Sharma AM. Use of beta-blockers in obesity hypertension: potential role of weight gain. *Obes Rev*. 2001;2(4):275–280. https://doi.org/10.1046/j.1467-789x.2001.00044.x.
229. Sharma AM, Pischon T, Hardt S, Kunz I, Luft FC. Hypothesis: beta-adrenergic receptor blockers and weight gain: a systematic analysis. *Hypertension*. 2001;37(2):250–254. https://doi.org/10.1161/01.hyp.37.2.250.
230. Mazidi M, Rezaie P, Gao HK, Kengne AP. Effect of sodium-glucose cotransport-2 inhibitors on blood pressure in people with type 2 diabetes mellitus: a systematic review and meta-analysis of 43 randomized control trials with 22 528 patients. *J Am Heart Assoc*. 2017;6(6):e004007. https://doi.org/10.1161/jaha.116.004007.
231. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. *J Am Soc Hypertens*. 2014;8(4):262–275.e9. https://doi.org/10.1016/j.jash.2014.01.007.
232. Sun F, Wu S, Guo S, et al. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Res Clin Pract*. 2015;110(1):26–37. https://doi.org/10.1016/j.diabres.2015.07.015.
233. Berra C, Manfrini R, Regazzoli D, et al. Blood pressure control in type 2 diabetes mellitus with arterial hypertension. The important ancillary role of SGLT2-inhibitors and GLP1-receptor agonists. *Pharmacol Res*. 2020;160:105052. https://doi.org/10.1016/j.phrs.2020.105052.
234. Diallo A, Carlos-Bolumbu M, Galtier F. Blood pressure-lowering effects of SGLT2 inhibitors and GLP-1 receptor agonists for preventing of cardiovascular events and death in type 2 diabetes: a systematic review and meta-analysis. *Acta Diabetol*. 2023;60(12):1651–1662. https://doi.org/10.1007/s00592-023-02154-4.
235. Zhang Q, Zhou S, Liu L. Efficacy and safety evaluation of SGLT2i on blood pressure control in patients with type 2 diabetes and hypertension: a new meta-analysis. *Diabetol Metab Syndr*. 2023;15(1):118. https://doi.org/10.1186/s13098-023-01092-z.
236. Raghavan S, Vassy JL, Ho YL, et al. Diabetes mellitus-related all-cause and cardiovascular mortality in a national cohort of adults. *J Am Heart Assoc*. 2019;8(4):e011295. https://doi.org/10.1161/jaha.118.011295.
237. Doycheva I, Cui J, Nguyen P, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. *Aliment Pharmacol Ther*. 2016;43(1):83–95. https://doi.org/10.1111/apt.13405.
238. Cusi K, Sanyal AJ, Zhang S, et al. Non-alcoholic fatty liver disease (NAFLD) prevalence and its metabolic associations in patients with type 1 diabetes and type 2 diabetes. *Diabetes Obes Metab*. 2017;19(11):1630–1634. https://doi.org/10.1111/dom.12973.
239. Beghini A, Sammartino AM, Papp Z, et al. 2024 update in heart failure. *ESC Heart Fail*. 2025;12(1):8–42. https://doi.org/10.1002/ehf2.14857.
240. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413–1424. https://doi.org/10.1056/NEJMoa2022190.
241. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451–1461. https://doi.org/10.1056/NEJMoa2107038.
242. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387(12):1089–1098. https://doi.org/10.1056/NEJMoa2206286.
243. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995–2008. https://doi.org/10.1056/NEJMoa1911303.
244. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644–657. https://doi.org/10.1056/NEJMoa1611925.
245. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117–2128. https://doi.org/10.1056/NEJMoa1504720.
246. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347–357. https://doi.org/10.1056/NEJMoa1812389.
247. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol*. 2021;6(2):148–158. https://doi.org/10.1001/jamacardio.2020.4511.
248. Aggarwal R, Bhatt DL, Szarek M, et al. Effect of sotagliflozin on major adverse cardiovascular events: a prespecified secondary analysis of the SCORED randomised trial. *Lancet Diabetes Endocrinol*. 2025;13(4):321–332. https://doi.org/10.1016/s2213-8587(24)00362-0.
249. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021;9(10):653–662. https://doi.org/10.1016/s2213-8587(21)00203-5.
250. Margulies KB, Hernandez AF, Redfield MM, et al. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA*. 2016;316(5):500–508. https://doi.org/10.1001/jama.2016.10260.
251. Jorsal A, Kistorp C, Holmager P, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. *Eur J Heart Fail*. 2017;19(1):69–77. https://doi.org/10.1002/ejhf.657.
252. Zile MR, Borlaug BA, Kramer CM, et al. Effects of tirzepatide on the clinical trajectory of patients with heart failure, preserved ejection fraction, and obesity. *Circulation*. 2025;151(10):656–668. https://doi.org/10.1161/circulationaha.124.072679.
253. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317–1326. https://doi.org/10.1056/NEJMoa1307684.
254. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet*. 2015;385(9982):2067–2076. https://doi.org/10.1016/s0140-6736(14)62225-x.
255. Giugliano D, Longo M, Signoriello S, et al. The effect of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors on cardiorenal outcomes: a network meta-analysis of 23 CVOTs. *Cardiovasc Diabetol*. 2022;21(1):42. https://doi.org/10.1186/s12933-022-01474-z.
256. U.S. Food and Drug Administration. Actos (pioglitazone hydrochloride) prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s044lbl.pdf. Accessed January 31, 2023.
257. Schroeder EB, Powers JD, O'Connor PJ, et al. Prevalence of chronic kidney disease among individuals with diabetes in the SUPREME-DM project, 2005-2011. *J Diabetes Complications*. 2015;29(5):637–643. https://doi.org/10.1016/j.jdiacomp.2015.04.007.
258. U.S. Food and Drug Administration. Jardiance (empagliflozin tablets), for oral use, prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204629s042lbl.pdf; Updated June 2023. Accessed January 7, 2026.
259. U.S. Food and Drug Administration. Farxiga (dapagliflozin tablets), for oral use, prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202293s026lbl.pdf; Updated May 2023. Accessed January 7, 2026.
260. U.S. Food and Drug Administration. Invokana (canagliflozin tablets), for oral use, prescribing information. https://www.accessdata.fda.gov/drugsatfda_

docs/label/2018/204042s027lbl.pdf; Updated October 2018. Accessed January 7, 2026.
261. U.S. Food and Drug Administration. Steglatro (ertugliflozin) tablets, for oral use, prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209803s004lbl.pdf; Updated September 2021. Accessed January 7, 2026.
262. Zannad F, Ferreira JP, Pocock SJ, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from EMPEROR-Reduced. *Circulation*. 2021;143(4):310–321. https://doi.org/10.1161/circulationaha.120.051685.
263. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295–2306. https://doi.org/10.1056/NEJMoa1811744.
264. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436–1446. https://doi.org/10.1056/NEJMoa2024816.
265. Heerspink HJL, Jongs N, Chertow GM, et al. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol*. 2021;9(11):743–754. https://doi.org/10.1016/s2213-8587(21)00242-4.
266. Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388(2):117–127. https://doi.org/10.1056/NEJMoa2204233.
267. Agarwal R, Green JB, Heerspink HJL, et al. Finerenone with empagliflozin in chronic kidney disease and type 2 diabetes. *N Engl J Med*. 2025;393(6):533–543. https://doi.org/10.1056/NEJMoa2410659.
268. Chuang MH, Wang HY, Kan WC, et al. Cardio-kidney outcomes for combined versus monotherapy with finerenone or SGLT2 inhibitors in patients with CKD. *Nephrol Dial Transplant*. 2025;40(10):1897–1905. https://doi.org/10.1093/ndt/gfaf064.
269. Hanouneh M, Le D, Jaar BG, Tamargo C, Cervantes CE. Real-life experience on the effect of SGLT2 inhibitors vs. finerenone vs. combination on albuminuria in chronic kidney disease. *Diagnostics (Basel)*. 2024;14(13):1357. https://doi.org/10.3390/diagnostics14131357.
270. Mann JFE, Fonseca V, Mosenzon O, et al. Effects of liraglutide versus placebo on cardiovascular events in patients with type 2 diabetes mellitus and chronic kidney disease. *Circulation*. 2018;138(25):2908–2918. https://doi.org/10.1161/circulationaha.118.036418.
271. Mann JFE, Fonseca VA, Poulter NR, et al. Safety of liraglutide in type 2 diabetes and chronic kidney disease. *Clin J Am Soc Nephrol*. 2020;15(4):465–473. https://doi.org/10.2215/cjn.11881019.
272. Shaman AM, Bain SC, Bakris GL, et al. Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: pooled analysis of SUSTAIN 6 and LEADER. *Circulation*. 2022;145(8):575–585. https://doi.org/10.1161/circulationaha.121.055459.
273. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834–1844. https://doi.org/10.1056/NEJMoa1607141.
274. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311–322. https://doi.org/10.1056/NEJMoa1603827.
275. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121–130. https://doi.org/10.1016/s0140-6736(19)31149-3.
276. Lee MMY, Sattar N, Pop-Busui R, et al. Cardiovascular and kidney outcomes and mortality with long-acting injectable and oral glucagon-like peptide 1 receptor agonists in individuals with type 2 diabetes: a systematic review and meta-analysis of randomized trials. *Diabetes Care*. 2025;48(5):846–859. https://doi.org/10.2337/dc25-0241.
277. Neuen BL, Fletcher RA, Heath L, et al. Cardiovascular, kidney, and safety outcomes with GLP-1 receptor agonists alone and in combination with SGLT2 inhibitors in type 2 diabetes: a systematic review and meta-analysis. *Circulation*. 2024;150(22):1781–1790. https://doi.org/10.1161/circulationaha.124.071689.
278. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet*. 2019;394(10193):131–138. https://doi.org/10.1016/s0140-6736(19)31150-x.
279. Lilly's Mounjaro (tirzepatide), a GIP/GLP-1 dual agonist, demonstrated cardiovascular protection in landmark head-to-head trial, reinforcing its benefit in patients with type 2 diabetes and heart disease. https://investor.lilly.com/news-releases/news-release-details/lillys-mounjaro-tirzepatide-gipglp-1-dual-agonist-demonstrated. Accessed October 12, 2025.
280. Nicholls SJ, Pavo I, Bhatt DL, et al. Cardiovascular outcomes with tirzepatide versus dulaglutide in type 2 diabetes. *N Engl J Med*. 2025;393(24):2409–2420. https://doi.org/10.1056/NEJMoa2505928.
281. Mannucci E, Mosenzon O, Avogaro A. Analyses of results from cardiovascular safety trials with DPP-4 inhibitors: cardiovascular outcomes, predefined safety outcomes, and pooled analysis and meta-analysis. *Diabetes Care*. 2016;39(Suppl 2):S196–S204. https://doi.org/10.2337/dcS15-3024.
282. Wu S, Hopper I, Skiba M, Krum H. Dipeptidyl peptidase-4 inhibitors and cardiovascular outcomes: meta-analysis of randomized clinical trials with 55,141 participants. *Cardiovasc Ther*. 2014;32(4):147–158. https://doi.org/10.1111/1755-5922.12075.
283. Ren Z, Fu X. Stroke risk factors in United States: an analysis of the 2013-2018 National Health and Nutrition Examination Survey. *Int J Gen Med*. 2021;14:6135–6147. https://doi.org/10.2147/ijgm.S327075.
284. Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2020;76(9):1117–1145. https://doi.org/10.1016/j.jacc.2020.05.037.
285. Grewal S, Zaman N, Borgatta L, Nudy M, Foy AJ, Peterson B. Usefulness of glucagon-like peptide-1 receptor agonists to reduce adverse cardiovascular disease events in patients with type 2 diabetes mellitus. *Am J Cardiol*. 2021;154:48–53. https://doi.org/10.1016/j.amjcard.2021.05.043.
286. Malhotra K, Katsanos AH, Lambadiari V, et al. GLP-1 receptor agonists in diabetes for stroke prevention: a systematic review and meta-analysis. *J Neurol*. 2020;267(7):2117–2122. https://doi.org/10.1007/s00415-020-09813-4.
287. Young LH, Viscoli CM, Curtis JP, et al. Cardiac outcomes after ischemic stroke or transient ischemic attack: effects of pioglitazone in patients with insulin resistance without diabetes mellitus. *Circulation*. 2017;135(20):1882–1893. https://doi.org/10.1161/circulationaha.116.024863.
288. Lee M, Saver JL, Liao HW, Lin CH, Ovbiagele B. Pioglitazone for secondary stroke prevention: a systematic review and meta-analysis. *Stroke*. 2017;48(2):388–393. https://doi.org/10.1161/strokeaha.116.013977.
289. Spence JD, Viscoli CM, Inzucchi SE, et al. Pioglitazone therapy in patients with stroke and prediabetes: a post hoc analysis of the IRIS randomized clinical trial. *JAMA Neurol*. 2019;76(5):526–535. https://doi.org/10.1001/jamaneurol.2019.0079.
290. Yaghi S, Furie KL, Viscoli CM, et al. Pioglitazone prevents stroke in patients with a recent transient ischemic attack or ischemic stroke: a planned secondary analysis of the IRIS Trial (Insulin Resistance Intervention After Stroke). *Circulation*. 2018;137(5):455–463. https://doi.org/10.1161/circulationaha.117.030458.
291. Spence JD, Viscoli C, Kernan WN, et al. Efficacy of lower doses of pioglitazone after stroke or transient ischaemic attack in patients with insulin resistance. *Diabetes Obes Metab*. 2022;24(6):1150–1158. https://doi.org/10.1111/dom.14687.
292. Zhou Z, Jardine MJ, Li Q, et al. Effect of SGLT2 inhibitors on stroke and atrial fibrillation in diabetic kidney disease: results from the CREDENCE trial and meta-analysis. *Stroke*. 2021;52(5):1545–1556. https://doi.org/10.1161/strokeaha.120.031623.
293. Tsai WH, Chuang SM, Liu SC, et al. Effects of SGLT2 inhibitors on stroke and its subtypes in patients with type 2 diabetes: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):15364. https://doi.org/10.1038/s41598-021-94945-4.
294. Younossi ZM, Golabi P, Price JK, et al. The global epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among patients with type 2 diabetes. *Clin Gastroenterol Hepatol*. 2024;22(10):1999–2010.e8. https://doi.org/10.1016/j.cgh.2024.03.006.
295. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*. 2023;79(6):1542–1556. https://doi.org/10.1016/j.jhep.2023.06.003.
296. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol*. 2024;81(3):492–542. https://doi.org/10.1016/j.jhep.2024.04.031.
297. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): executive summary. *Diabetologia*. 2024;67(11):2375–2392. https://doi.org/10.1007/s00125-024-06196-3.
298. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *Obes Facts*. 2024;17(4):374–444. https://doi.org/10.1159/000539371.
299. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract*. 2022;28(5):528–562. https://doi.org/10.1016/j.eprac.2022.03.010.
300. Cusi K, Abdelmalek MF, Apovian CM, et al. Metabolic dysfunction-associated steatotic liver disease (MASLD) in people with diabetes: the need for screening and early intervention. A consensus report of the American Diabetes Association. *Diabetes Care*. 2025;48(7):1057–1082. https://doi.org/10.2337/dci24-0094.
301. Harrison SA, Bedossa P, Guy CD, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med*. 2024;390(6):497–509. https://doi.org/10.1056/NEJMoa2309000.

302. Isaacs SD, Farrelly FV, Brennan PN. Role of anti-diabetic medications in the management of MASLD. *Frontline Gastroenterology*. 2025;16:239–249.
303. Dutour A, Abdesselam I, Ancel P, et al. Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy. *Diabetes Obes Metab*. 2016;18(9):882–891. https://doi.org/10.1111/dom.12680.
304. Bołdys A, Bułdak Ł., Nicze M, Okopień B. Liraglutide reduces liver steatosis and improves metabolic indices in obese patients without diabetes: a 3-month prospective study. *Int J Mol Sci*. 2025;26(12):5883. https://doi.org/10.3390/ijms26125883.
305. Kuchay MS, Krishan S, Mishra SK, et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). *Diabetologia*. 2020;63(11):2434–2445. https://doi.org/10.1007/s00125-020-05265-7.
306. Loomba R, Abdelmalek MF, Armstrong MJ, et al. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol Hepatol*. 2023;8(6):511–522. https://doi.org/10.1016/s2468-1253(23)00068-7.
307. Kongmalai T, Srinonprasert V, Anothaisintawee T, et al. New anti-diabetic agents for the treatment of non-alcoholic fatty liver disease: a systematic review and network meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)*. 2023;14:1182037. https://doi.org/10.3389/fendo.2023.1182037.
308. Gu Y, Sun L, He Y, et al. Comparative efficacy of glucagon-like peptide 1 (GLP-1) receptor agonists, pioglitazone and vitamin E for liver histology among patients with nonalcoholic fatty liver disease: systematic review and pilot network meta-analysis of randomized controlled trials. *Expert Rev Gastroenterol Hepatol*. 2023;17(3):273–282. https://doi.org/10.1080/17474124.2023.2172397.
309. Arredouani A. Time to approve glucagon-like peptide-1 receptor agonists for MASLD: a rational step based on robust evidence. *Diabetologia*. 2025;68(10):2296–2298. https://doi.org/10.1007/s00125-025-06527-y.
310. Harrison SA, Browne SK, Suschak JJ, et al. Effect of pemvidutide, a GLP-1/glucagon dual receptor agonist, on MASLD: a randomized, double-blind, placebo-controlled study. *J Hepatol*. 2025;82(1):7–17. https://doi.org/10.1016/j.jhep.2024.07.006.
311. Sanyal AJ, Bedossa P, Fraessdorf M, et al. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N Engl J Med*. 2024;391(4):311–319. https://doi.org/10.1056/NEJMoa2401755.
312. Romero-Gómez M, Lawitz E, Shankar RR, et al. A phase IIa active-comparator-controlled study to evaluate the efficacy and safety of efinopegdutide in patients with non-alcoholic fatty liver disease. *J Hepatol*. 2023;79(4):888–897. https://doi.org/10.1016/j.jhep.2023.05.013.
313. Sanyal AJ, Kaplan LM, Frias JP, et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. *Nat Med*. 2024;30(7):2037–2048. https://doi.org/10.1038/s41591-024-03018-2.
314. Lian J, Fu J. Pioglitazone for NAFLD patients with prediabetes or type 2 diabetes mellitus: a meta-analysis. *Front Endocrinol (Lausanne)*. 2021;12:615409. https://doi.org/10.3389/fendo.2021.615409.
315. Wang Z, Du H, Zhao Y, et al. Response to pioglitazone in non-alcoholic fatty liver disease patients with vs. without type 2 diabetes: a meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)*. 2023;14:1111430. https://doi.org/10.3389/fendo.2023.1111430.
316. Aithal GP, Thomas JA, Kaye PV, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology*. 2008;135(4):1176–1184. https://doi.org/10.1053/j.gastro.2008.06.047.
317. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med*. 2010;362(18):1675–1685. https://doi.org/10.1056/NEJMoa0907929.
318. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med*. 2016;165(5):305–315. https://doi.org/10.7326/m15-1774.
319. Bril F, Biernacki DM, Kalavalapalli S, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care*. 2019;42(8):1481–1488. https://doi.org/10.2337/dc19-0167.
320. Huang JF, Dai CY, Huang CF, et al. First-in-Asian double-blind randomized trial to assess the efficacy and safety of insulin sensitizer in nonalcoholic steatohepatitis patients. *Hepatol Int*. 2021;15(5):1136–1147. https://doi.org/10.1007/s12072-021-10242-2.
321. Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. *JAMA Intern Med*. 2017;177(5):633–640. https://doi.org/10.1001/jamainternmed.2016.9607.
322. Weng MT, Yang PJ, Liu PF, et al. Effects of dapagliflozin on liver steatosis in patients with nonalcoholic fatty liver disease: a randomized controlled trial. *Hepatol Int*. 2025;19(2):405–414. https://doi.org/10.1007/s12072-024-10758-3.
323. Latva-Rasku A, Honka MJ, Kullberg J, et al. The SGLT2 inhibitor dapagliflozin reduces liver fat but does not affect tissue insulin sensitivity: a randomized, double-blind, placebo-controlled study with 8-week treatment in type 2 diabetes patients. *Diabetes Care*. 2019;42(5):931–937. https://doi.org/10.2337/dc18-1569.
324. Hiruma S, Shigiyama F, Kumashiro N. Empagliflozin versus sitagliptin for ameliorating intrahepatic lipid content and tissue-specific insulin sensitivity in patients with early-stage type 2 diabetes with non-alcoholic fatty liver disease: a prospective randomized study. *Diabetes Obes Metab*. 2023;25(6):1576–1588. https://doi.org/10.1111/dom.15006.
325. Kahl S, Gancheva S, Straßburger K, et al. Empagliflozin effectively lowers liver fat content in well-controlled type 2 diabetes: a randomized, double-blind, phase 4, placebo-controlled trial. *Diabetes Care*. 2020;43(2):298–305. https://doi.org/10.2337/dc19-0641.
326. Borisov AN, Kutz A, Christ ER, Heim MH, Ebrahimi F. Canagliflozin and metabolic associated fatty liver disease in patients with diabetes mellitus: new insights from CANVAS. *J Clin Endocrinol Metab*. 2023;108(11):2940–2949. https://doi.org/10.1210/clinem/dgad249.
327. Corbin KD, Dagogo-Jack S, Cannon CP, et al. Cardiorenal outcomes by indices of liver steatosis and fibrosis in individuals with type 2 diabetes and atherosclerotic cardiovascular disease: analyses from VERTIS CV, a randomized trial of the sodium-glucose cotransporter-2 inhibitor ertugliflozin. *Diabetes Obes Metab*. 2023;25(3):758–766. https://doi.org/10.1111/dom.14923.
328. Lin J, Huang Y, Xu B, et al. Effect of dapagliflozin on metabolic dysfunction-associated steatohepatitis: multicentre, double blind, randomised, placebo controlled trial. *BMJ*. 2025;389:e083735. https://doi.org/10.1136/bmj-2024-083735.
329. Fralick M, Redelmeier DA, Patorno E, et al. Identifying risk factors for diabetic ketoacidosis associated with SGLT2 inhibitors: a nationwide cohort study in the USA. *J Gen Intern Med*. 2021;36(9):2601–2607. https://doi.org/10.1007/s11606-020-06561-z.
330. Blonde L, Stenlöf K, Fung A, Xie J, Canovatchel W, Meininger G. Effects of canagliflozin on body weight and body composition in patients with type 2 diabetes over 104 weeks. *Postgrad Med*. 2016;128(4):371–380. https://doi.org/10.1080/00325481.2016.1169894.
331. Cheong AJY, Teo YN, Teo YH, et al. SGLT inhibitors on weight and body mass: A meta-analysis of 116 randomized-controlled trials. *Obesity (Silver Spring)*. 2022;30(1):117–128. https://doi.org/10.1002/oby.23331.
332. Kovacs CS, Seshiah V, Swallow R, et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. *Diabetes Obes Metabol*. 2014;16(2):147–158. https://doi.org/10.1111/dom.12188.
333. Abdul-Ghani M, Puckett C, Adams J, et al. Durability of triple combination therapy versus stepwise addition therapy in patients with new-onset T2DM: 3-year follow-up of EDICT. *Diabetes Care*. 2021;44(2):433–439. https://doi.org/10.2337/dc20-0978.
334. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet*. 2019;394(10208):1519–1529. https://doi.org/10.1016/s0140-6736(19)32131-2.
335. Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2013;1(1):28–34. https://doi.org/10.1016/s2213-8587(13)70006-8.
336. Mannucci E, Caiulo C, Naletto L, Madama G, Monami M. Efficacy and safety of different basal and prandial insulin analogues for the treatment of type 2 diabetes: a network meta-analysis of randomized controlled trials. *Endocrine*. 2021;74(3):508–517. https://doi.org/10.1007/s12020-021-02889-6.
337. Men P, Qu S, Luo W, Li C, Zhai S. Comparison of lixisenatide in combination with basal insulin vs other insulin regimens for the treatment of patients with type 2 diabetes inadequately controlled by basal insulin: systematic review, network meta-analysis and cost-effectiveness analysis. *Diabetes Obes Metab*. 2020;22(1):107–115. https://doi.org/10.1111/dom.13871.
338. Yki-Järvinen H, Juurinen L, Alvarsson M, et al. Initiate Insulin by Aggressive Titration and Education (INITIATE): a randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups. *Diabetes Care*. 2007;30(6):1364–1369. https://doi.org/10.2337/dc06-1357.
339. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26(11):3080–3086. https://doi.org/10.2337/diacare.26.11.3080.
340. Mathieu C, Ásbjörnsdóttir B, Bajaj HS, et al. Switching to once-weekly insulin icodec versus once-daily insulin glargine U100 in individuals with basal-bolus insulin-treated type 2 diabetes (ONWARDS 4): a phase 3a, randomised, open-label, multicentre, treat-to-target, non-inferiority trial. *Lancet*. 2023;401(10392):1929–1940. https://doi.org/10.1016/s0140-6736(23)00520-2.
341. Rosenstock J, Bain SC, Gowda A, et al. Weekly icodec versus daily glargine U100 in type 2 diabetes without previous insulin. *N Engl J Med*. 2023;389(4):297–308. https://doi.org/10.1056/NEJMoa2303208.
342. Philis-Tsimikas A, Asong M, Franek E, et al. Switching to once-weekly insulin icodec versus once-daily insulin degludec in individuals with basal insulin-

treated type 2 diabetes (ONWARDS 2): a phase 3a, randomised, open label, multicentre, treat-to-target trial. *Lancet Diabetes Endocrinol*. 2023;11(6):414–425. https://doi.org/10.1016/s2213-8587(23)00093-1.
343. Mathieu C, Giorgino F, Kim SG, et al. Once-weekly IcoSema versus once-weekly insulin icodec in type 2 diabetes management (COMBINE 1): an open-label, multicentre, treat-to-target, randomised, phase 3a trial. *Lancet Diabetes Endocrinol*. 2025;13(7):568–579. https://doi.org/10.1016/s2213-8587(25)00096-8.
344. Billings LK, Andreozzi F, Frederiksen M, et al. Once-weekly IcoSema versus multiple daily insulin injections in type 2 diabetes management (COMBINE 3): an open-label, multicentre, treat-to-target, non-inferiority, randomised, phase 3a trial. *Lancet Diabetes Endocrinol*. 2025;13(7):556–567. https://doi.org/10.1016/s2213-8587(25)00052-x.
345. Wysham C, Bajaj HS, Del Prato S, et al. Insulin efsitora versus degludec in type 2 diabetes without previous insulin treatment. *N Engl J Med*. 2024;391(23):2201–2211. https://doi.org/10.1056/NEJMoa2403953.
346. Cowart K. Overbasalization: addressing hesitancy in treatment intensification beyond basal insulin. *Clin Diabetes*. 2020;38(3):304–310. https://doi.org/10.2337/cd19-0061.
347. Zisman A, Morales F, Stewart J, Stuhr A, Vlajnic A, Zhou R. BeAM value: an indicator of the need to initiate and intensify prandial therapy in patients with type 2 diabetes mellitus receiving basal insulin. *BMJ Open Diabetes Res Care*. 2016;4(1):e000171. https://doi.org/10.1136/bmjdrc-2015-000171.
348. Owens DR, Luzio SD, Sert-Langeron C, Riddle MC. Effects of initiation and titration of a single pre-prandial dose of insulin glulisine while continuing titrated insulin glargine in type 2 diabetes: a 6-month 'proof-of-concept' study. *Diabetes Obes Metab*. 2011;13(11):1020–1027. https://doi.org/10.1111/j.1463-1326.2011.01459.x.
349. Lankisch MR, Ferlinz KC, Leahy JL, Scherbaum WA. Introducing a simplified approach to insulin therapy in type 2 diabetes: a comparison of two single-dose regimens of insulin glulisine plus insulin glargine and oral antidiabetic drugs. *Diabetes Obes Metab*. 2008;10(12):1178–1185. https://doi.org/10.1111/j.1463-1326.2008.00967.x.
350. Vora J, Cohen N, Evans M, Hockey A, Speight J, Whately-Smith C. Intensifying insulin regimen after basal insulin optimization in adults with type 2 diabetes: a 24-week, randomized, open-label trial comparing insulin glargine plus insulin glulisine with biphasic insulin aspart (LanScape). *Diabetes Obes Metab*. 2015;17(12):1133–1141. https://doi.org/10.1111/dom.12528.
351. Carlson JN, Schunder-Tatzber S, Neilson CJ, Hood N. Dietary sugars versus glucose tablets for first-aid treatment of symptomatic hypoglycaemia in awake patients with diabetes: a systematic review and meta-analysis. *Emerg Med J*. 2017;34(2):100–106. https://doi.org/10.1136/emermed-2015-205637.
352. Newswanger B, Ammons S, Phadnis N, et al. Development of a highly stable, nonaqueous glucagon formulation for delivery via infusion pump systems. *J Diabetes Sci Technol*. 2015;9(1):24–33. https://doi.org/10.1177/1932296814565131.
353. Hövelmann U, Bysted BV, Mouritzen U, et al. Pharmacokinetic and pharmacodynamic characteristics of dasiglucagon, a novel soluble and stable glucagon analog. *Diabetes Care*. 2018;41(3):531–537. https://doi.org/10.2337/dc17-1402.
354. Christiansen MP, Cummins M, Prestrelski S, Close NC, Nguyen A, Junaidi K. Comparison of a ready-to-use liquid glucagon injection administered by autoinjector to glucagon emergency kit for the symptomatic relief of severe hypoglycemia: two randomized crossover non-inferiority studies. *BMJ Open Diabetes Res Care*. 2021;9(1):e002137. https://doi.org/10.1136/bmjdrc-2021-002137.
355. Rickels MR, Ruedy KJ, Foster NC, et al. Intranasal glucagon for treatment of insulin-induced hypoglycemia in adults with type 1 diabetes: a randomized crossover noninferiority study. *Diabetes Care*. 2016;39(2):264–270. https://doi.org/10.2337/dc15-1498.
356. Pontiroli AE. Intranasal glucagon: a promising approach for treatment of severe hypoglycemia. *J Diabetes Sci Technol*. 2015;9(1):38–43. https://doi.org/10.1177/1932296814557518.
357. Sherr JL, Ruedy KJ, Foster NC, et al. Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. *Diabetes Care*. 2016;39(4):555–562. https://doi.org/10.2337/dc15-1606.
358. U.S. Food and Drug Administration. Baqsimi (glucagon) nasal powder prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210134s000lbl.pdf. Accessed November 28, 2022.
359. Amaro A, Sugimoto D, Wharton S. Efficacy and safety of semaglutide for weight management: evidence from the STEP program. *Postgrad Med*. 2022;134(Sup1):5–17. https://doi.org/10.1080/00325481.2022.2147326.
360. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA*. 2015;314(7):687–699. https://doi.org/10.1001/jama.2015.9676.
361. De Block C, Bailey C, Wysham C, Hemmingway A, Allen SE, Peleshok J. Tirzepatide for the treatment of adults with type 2 diabetes: an endocrine perspective. *Diabetes Obes Metab*. 2023;25(1):3–17. https://doi.org/10.1111/dom.14831.
362. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376(9741):595–605. https://doi.org/10.1016/s0140-6736(10)60888-4.
363. Hollander P, Gupta AK, Plodkowski R, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care*. 2013;36(12):4022–4029. https://doi.org/10.2337/dc13-0234.
364. Li Z, Hong K, Yip I, et al. Body weight loss with phentermine alone versus phentermine and fenfluramine with very-low-calorie diet in an outpatient obesity management program: a retrospective study. *Curr Ther Res Clin Exp*. 2003;64(7):447–460. https://doi.org/10.1016/s0011-393x(03)00126-7.
365. Miles JM, Leiter L, Hollander P, et al. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. *Diabetes Care*. 2002;25(7):1123–1128. https://doi.org/10.2337/diacare.25.7.1123.
366. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet*. 2018;392(10148):637–649. https://doi.org/10.1016/s0140-6736(18)31773-2.
367. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. *Int J Obes Relat Metab Disord*. 2003;27(12):1437–1446. https://doi.org/10.1038/sj.ijo.0802475.
368. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5(4):251–260. https://doi.org/10.1016/s2213-8587(17)30013-x.
369. Chang Jin C, Kyung-Soo K, Sung Rae K, Jae Heon K, Hye Soon P. Double-blind, parallel-group, placebo-controlled multi-center clinical trial for evaluating the efficacy and safety of phentermine hydrochloride in obese patients. *Korean J Obes*. 2005;14(3):155–162.
370. Casanova L, Gobin N, Villani P, Verger P. Bias in the measure of the effectiveness of seasonal influenza vaccination among diabetics. *Prim Care Diabetes*. 2016;10(6):398–406. https://doi.org/10.1016/j.pcd.2016.05.005.
371. Smith SA, Poland GA. Use of influenza and pneumococcal vaccines in people with diabetes. *Diabetes Care*. 2000;23(1):95–108. https://doi.org/10.2337/diacare.23.1.95.
372. Gregory JM, Slaughter JC, Duffus SH, et al. COVID-19 severity is tripled in the diabetes community: A -prospective analysis of the -pandemic's impact in type 1 and type 2 diabetes. *Diabetes Care*. 2021;44(2):526–532. https://doi.org/10.2337/dc20-2260.
373. Dos Santos G, Tahrat H, Bekkat-Berkani R. Immunogenicity, safety, and effectiveness of seasonal influenza vaccination in patients with diabetes mellitus: a systematic review. *Hum Vaccin Immunother*. 2018;14(8):1853–1866. https://doi.org/10.1080/21645515.2018.1446719.
374. Lu PJ, Hung MC, Srivastav A, et al. Surveillance of vaccination coverage among adult populations -United States, 2018. *MMWR Surveill Summ*. 2021;70(3):1–26. https://doi.org/10.15585/mmwr.ss7003a1.
375. Hurley LP, Bridges CB, Harpaz R, et al. U.S. physicians' perspective of adult vaccine delivery. *Ann Intern Med*. 2014;160(3):161. https://doi.org/10.7326/m13-2332.
376. U.S. National Vaccine Advisory Committee. Recommendations from the National Vaccine Advisory Committee: standards for adult immunization practice. *Public Health Rep*. 2014;129(2):115–123. https://doi.org/10.1177/003335491412900203.
377. U.S. Centers for Disease Control and Prevention. Standards for adult immunization practice. https://www.cdc.gov/vaccines/hcp/adults/for-practice/standards/index.html. Accessed November 10, 2022.
378. Jacobson Vann JC, Jacobson RM, Coyne-Beasley T, Asafu-Adjei JK, Szilagyi PG. Patient reminder and recall interventions to improve immunization rates. *Cochrane Database Syst Rev*. 2018;1(1):CD003941. https://doi.org/10.1002/14651858.CD003941.pub3.
379. Johnson DR, Nichol KL, Lipczynski K. Barriers to adult immunization. *Am J Med*. 2008;121(7 Suppl 2):S28–S35. https://doi.org/10.1016/j.amjmed.2008.05.005.
380. Nowalk MP, Moehling KK, Zhang S, Raviotta JM, Zimmerman RK, Lin CJ. Using the 4 pillars to increase vaccination among high-risk adults: who benefits? *Am J Manag Care*. 2017;23(11):651–655.